

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666**

**CORRESPONDENCE**

**BEECHAM**



**PHARMACEUTICALS**

*DIVISION OF BEECHAM INC.*

65 INDUSTRIAL SOUTH • CLIFTON, NEW JERSEY 07012 • Phone (201) 778-9000

May 20, 1969

Mr. Robert C. Brandenburg  
Director of Certification Services (CC-100)  
Food and Drug Administration  
Department of Health, Education and Welfare  
200 "C" Street - S. W.  
Washington, D. C. 20204

Dear Mr. Brandenburg:

In accordance with regulations promulgated under Section 507 of the Federal Food, Drug and Cosmetic Act, as amended, we hereby submit this application with respect to Totacillin (Ampicillin Trihydrate) Oral Suspension.

We are transmitting herewith, in triplicate, Beecham Pharmaceuticals' Form 6 for the manufacture, packaging and control of Ampicillin Trihydrate Oral Suspension. Totacillin Oral Suspension will be marketed in 125 mg./5 cc. and 250 mg./5 cc. dosage forms. The Suspensions will be packaged in 80 cc. and 150 cc. presentations. The Administration is hereby advised that information pertaining to the manufacture, processing and control of the Bulk Ampicillin Trihydrate may be found in Beecham Pharmaceuticals' Form 1675, approved by the Administration on August 31, 1967. Both the Bulk Ampicillin Trihydrate and the finished Oral Suspension dosage forms will be manufactured by Beecham Pharmaceuticals, at their facility in Piscataway, New Jersey. 18782

We hereby submit with this submission a request for a 12-month expiration date on Totacillin Ampicillin Trihydrate Oral Suspension, for which stability data has been included.

This submission also contains blood and uring level data for Totacillin Ampicillin Trihydrate Oral Suspension. The clinical studies, monitored by our Medical Director, conclude that the formulations presented within this submission are comparable to available formulations presently certified by the Food and Drug Administration.

We trust that the Administration will find this information in order and we sincerely appreciate its consideration at your earliest convenience.

Yours sincerely,

C. West, Ph. D.  
Vice-President, Production

may 23, 1969

In reply refer to 146a.118 & No. 60-666

Colin West, Ph.D.  
Vice-President, Production  
Beecham Pharmaceuticals  
65 Industrial South  
Clifton, New Jersey 07012

Dear Dr. West:

We acknowledge receipt of your Antibiotic Form 6 application submitted May 20, 1969, to provide for the manufacture of TOTACILLIN (ampicillin trihydrate) for Oral Suspension.

A copy of the application has been forwarded to our Division of Anti-Infective Drugs (Bureau of Medicine) for an evaluation on the blood and urine level data which have been presented.

At your earliest convenience we would like to receive 6 exhibit samples from each of — batches of each potency of the formulations you propose to market. The samples will be evaluated in our laboratories.

We have established a numerical identification system for our Form 6 files and have assigned number 60-666 to the application. All future correspondence pertaining to this Form 6 should refer to this number and to the antibiotic regulation - §146a.118 - under which the drug is eligible for certification.

Sincerely yours,

John D. Harrison  
Office of Certification  
Services

cc: CC-100  
CC-100 O/D

JDHarrison: jk

**BEECHAM**  **PHARMACEUTICALS**

DIVISION OF BEECHAM INC.

65 INDUSTRIAL SOUTH • CLIFTON, NEW JERSEY 07012 • Phone (201) 778-9000

July 2, 1969

Mr. John D. Harrison  
Office of Certification Services  
Food and Drug Administration  
Department of Health, Education and Welfare  
200 "C" Street - S. W. (CC-100)  
Washington, D. C. 20204

Re: 146a.118 - No. 660-666 Totacillin Ampicillin Trihydrate  
Oral Suspension

Dear Mr. Harrison:

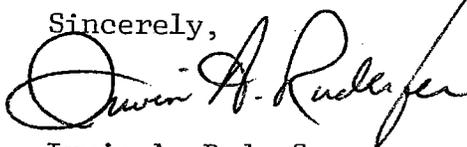
In accordance with requests made in your letter of May 23, 1969, we are transmitting herewith six (6) exhibit samples of Totacillin (ampicillin trihydrate) Oral Suspension from each of \_\_\_\_\_ batches of each potency of the formulation we propose to market for the Administration's analysis and evaluation.

We have included a certificate of analysis for each of the control numbers. The following samples are included:

	<u>Product</u>	<u>Potency</u>	<u>Control No.</u>	<u>No. of Samples</u>
m435	Totacillin (ampicillin trihydrate) Oral Suspension	125 mg/5 cc	60	3 bottles
m436	Totacillin (ampicillin trihydrate) Oral Suspension	125mg/5 cc	61	3 bottles
437	Totacillin (ampicillin trihydrate) Oral Suspension	125 mg/5 cc	72	3 bottles
438	Totacillin (ampicillin trihydrate) Oral Suspension	250 mg/5 cc	73	3 bottles
439	Totacillin (ampicillin trihydrate) Oral Suspension	250 mg/5 cc	75	3 bottles
440	Totacillin (ampicillin trihydrate) Oral Suspension	250 mg/5 cc	76	3 bottles

We trust you will find the enclosed samples in order and we sincerely appreciate your consideration of them, at your earliest convenience.

Sincerely,



Irwin A. Ruderfer  
Regulatory Liaison Administrator

1s  
Encs.

cc Dr. C. West

July 15, 1969

MEMORANDUM OF A TELEPHONE CONVERSATION

Between: Mr. Irwin Ruderfer

Beecham Laboratories,  
Clifton, New Jersey

and

William E. Dye, Ph.D.

Division of  
Anti-infective Drugs  
OND/DAD

Mr. Ruderfer called to inquire about the status of his firm's Form 6 application for ampicillin trihydrate for oral suspension, OCS Document No. 18782, NDA 60-666 and IND 5536. I told him that I had reviewed the data with Dr. Alan Smith of this Division, but that I wished to confer further before giving him my comments.

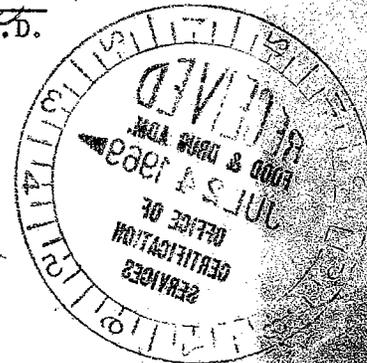
I saw Dr. Smith on the morning of the 16th and telephoned Mr. Ruderfer that, while the protocols for blood levels in children were generally satisfactory, the dosage employed (250 mg per child) was too high and that the experiments should be repeated with that dosage in milligrams per kilogram of body weight which was recommended in the labeling. Dr. Ruderfer did not comment on this, but said he would refer the matter to Dr. Chris Demos of Beecham who would probably contact Dr. Smith later.

*William E. Dye*  
William E. Dye, Ph.D.

cc:

- (OCS/CC-100) CD
- Dup. Form 6 (OCS/CC-100)
- OND/MD-100 OCS/CC-100/DO
- DAD/MD-140
- Med/MD-14
- WEDye/MD-140/mh1 7-15-69
- Typed: 7-18-69
- R/D init. by AESmith 7-18-69

*notes about Smith 7/22/69*



BEECHAM



PHARMACEUTICALS

DIVISION OF BEECHAM INC.

65 INDUSTRIAL SOUTH • CLIFTON, NEW JERSEY 07012 • Phone (201) 778-9000

November 3, 1969

Mr. Robert C. Brandenburg  
Director of Certification Services  
Food and Drug Administration (CC-100)  
Department of Health, Education, & Welfare  
200 "C" Street - S.W.  
Washington, D.C. 20204

Re: CFR 146a.118 No. 60-666 Totacillin ampicillin  
trihydrate for Oral Suspension

Dear Mr. Brandenburg:

We are transmitting herewith, in triplicate, an amendment to Beecham Pharmaceuticals' Form 6 (60-666) for Totacillin ampicillin trihydrate for Oral Suspension in the 125 mg/5cc and 250 mg/5cc dosage forms, which was originally submitted to the Administration on May 20, 1969.

This amendment consists of a revised master formulation for the product, excluding \_\_\_\_\_ as one of its components and increasing the batch size. The increase in batch size revision was necessitated by the installation of a \_\_\_\_\_ in our manufacturing process area.

The \_\_\_\_\_

The \_\_\_\_\_

Please note we have instituted a system of formulation using the bulk potency of the active ingredient rather than an assumed potency, as has been our previous practice.

We trust the Administration will find the enclosed information in order and we sincerely appreciate its consideration at your earliest convenience.

Sincerely,

Irwin A. Ruderfer

Regulatory Liaison Administrator

IAR:ms

cc: Dr. C. West

**BEECHAM**  **PHARMACEUTICALS**  
DIVISION OF BEECHAM INC.  
65 INDUSTRIAL SOUTH • CLIFTON, NEW JERSEY 07012 • Phone (201) 778-9000

November 24, 1969

Mr. Robert C. Brandenburg, Director  
Office of Certification Services (CC 100)  
Food and Drug Administration  
200 "C" Street - S.W.  
Washington, D.C. 20204

Re: Form 60-666 Totacillin ampicillin trihydrate for  
Oral Suspension (CFR 146a.118)

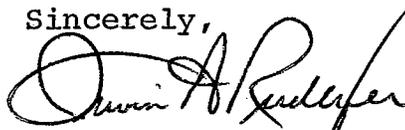
Dear Mr. Brandenburg:

We are transmitting herewith, in triplicate, an amendment to Beecham Pharmaceuticals' Form 60-666 for Totacillin ampicillin trihydrate for Oral Suspension, in the 125 mg/per 5cc and 250 mg/per 5cc dosage forms, originally submitted to the Administration on May 20, 1969.

This amendment consists of revised draft copy for the package insert and final specimens of the printed carton and label copy.

We trust that the Administration will find this information in order and we sincerely appreciate its consideration at your earliest convenience.

Sincerely,



Irwin A. Ruderfer  
Regulatory Liaison Administrator

IAR:ms

cc: Dr. C. West

H. S. Harrison

**BEECHAM** **p** **PHARMACEUTICALS**  
DIVISION OF BEECHAM INC.  
65 INDUSTRIAL SOUTH • CLIFTON, NEW JERSEY 07012 • Phone (201) 778-9000

December 23, 1969

Mr. Robert C. Brandenburg  
Director of Certification Services (CC-100)  
Food and Drug Administration  
Department of Health, Education, & Welfare  
200 "C" Street - S.W.  
Washington, D.C. 20204

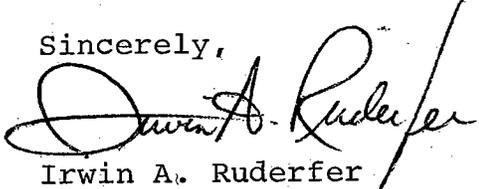
Re: Totacillin ampicillin trihydrate for Oral Suspension  
(CFR 146a.118) FORM 6-60-666

Dear Mr. Brandenburg:

In confirmation of our discussion with Drs. Smith and McQueen of the Bureau of Medicine today, we are transmitting herewith, in triplicate, revised insert copy for Totacillin ampicillin trihydrate for Oral Suspension, reflecting their suggestions.

00397

We trust that the Administration will find this information in order and we sincerely appreciate its consideration at your earliest convenience.

Sincerely,  
  
Irwin A. Ruderfer  
Regulatory Liaison Administrator

IAR:ms

cc: Dr. C. West

BEECHAM



PHARMACEUTICALS

DIVISION OF BEECHAM INC.

65 INDUSTRIAL SOUTH • CLIFTON, NEW JERSEY 07012 • Phone (201) 778-9000

February 19, 1970

Mr. Robert C. Brandenburg  
Director of Certification Services  
Food and Drug Administration  
Washington, D.C. 20204

Re: Form 60-666 Totacillin ampicillin trihydrate  
for Oral Suspension (146a.118)

Dear Mr. Brandenburg:

We are transmitting herewith, in triplicate, an amendment to Beecham Pharmaceuticals' Form 60-666 for Totacillin ampicillin trihydrate for Oral Suspension \_\_\_\_\_ in the 125 mg./5cc and 250 mg./5cc dosage forms.

This amendment consists of the clinical results and their statistical and graphic analyses. The clinical studies were monitored by our Medical Department. It was concluded that the Beecham -- Totacillin \_\_\_\_\_ Oral Suspension formulations, submitted to the Administration on November 3, 1969, are comparable to available formulations presently certified by the Food and Drug Administration.

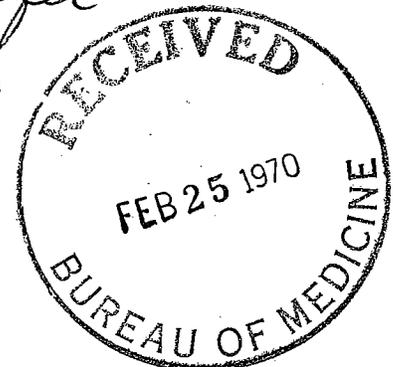
We trust the Administration will find this data in order and we sincerely appreciate its consideration at your earliest convenience.

Sincerely,

Irwin A. Ruderfer  
Regulatory Liaison  
Administrator

IAR:ms

cc: Dr. C. West  
Dr. C. Demos



BEECHAM



PHARMACEUTICALS

DIVISION OF BEECHAM INC.

65 INDUSTRIAL SOUTH • CLIFTON, NEW JERSEY 07012 • Phone (201) 778-9000

*AC*  
*File - moreplyne*  
*J. H. ...*  
*3/25/76*

February 25, 1970

Mr. Robert C. Brandenburg  
Director of Certification Services  
Food and Drug Administration (DHEW)  
5600 Fishers Lane  
Rockville, Maryland 20852

Re: Ampicillin Trihydrate for Oral Suspension  
Form 60-666 CFR 146a.118

Dear Mr. Brandenburg:

This is to authorize the Food and Drug Administration to refer to Beecham Pharmaceuticals' Totacillin<sup>R</sup> ampicillin trihydrate for Oral Suspension blood level study data submitted to the Administration on February 19, 1970 in support of the future filing by Beecham of labeling for Alpen<sup>R</sup> ampicillin trihydrate for Oral Suspension. Alpen Oral Suspension will be manufactured, packaged, controlled, and certified by Beecham Pharmaceuticals and distributed by Lederle Laboratories, Division of American Cyanamid Company.

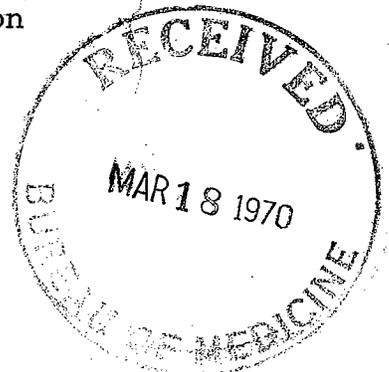
We sincerely appreciate the Administration's consideration of the above.

Sincerely,

Irwin A. Ruderfer  
Regulatory Liaison  
Administrator

IAR:ms

cc: Dr. C. West  
Mr. J.K. Rooney



1 copy ~~DD~~ 140  
22 Apr 70

Hand delivered by  
Dr. Colin West  
4/22/70  
Alan E. Smith

**BEECHAM**



**PHARMACEUTICALS**

DIVISION OF BEECHAM INC.

65 INDUSTRIAL SOUTH • CLIFTON, NEW JERSEY 07012 • Phone (201) 778-9000

A-6

April 21, 1970

~~James~~  
Eisler

Dr. Alan E. Smith  
Director  
Division of Anti-infective Drugs  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, Maryland 20852

Dear Dr. Smith:

We are transmitting herewith, in triplicate, an amendment to Beecham Pharmaceuticals' Form 60-666 for Totacillin ampicillin trihydrate for Oral Suspension in the 125 mg/5 cc and 250 mg/5 cc dosage forms. This labeling is a supplement to our submissions for this drug made on May 20, 1969 and on various dates up to February 19, 1970.

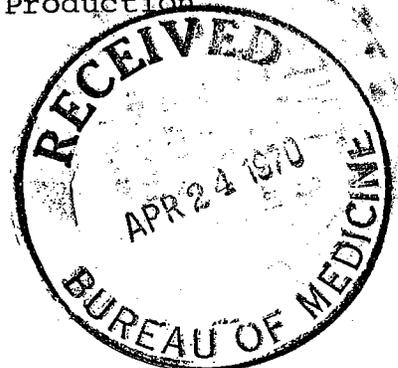
This labeling corresponds to the Administration's suggested revisions. We trust that this information taken together with the manufacturing data and blood level information previously submitted represents a complete filing for this drug. 01986

We trust that the Administration will find this information in order and we would be most grateful for your speedy approval of these dosage forms.

Yours sincerely,

C. West, Ph. D.  
Vice President  
Production

CW:rr



April 29, 1970

Our reference:  
60-666 (146a 118)

C. West, Ph.D.  
Vice President, Production  
Beecham Pharmaceuticals  
Division of Beecham, Inc.  
65 Industrial South  
Clifton, New Jersey 07012

Dear Dr. West:

Reference is made to your Form 6 (#60-666) dated May 20, 1969, and as supplemented on November 3, 1969, November 24, 1969, December 23, 1969, February 19, 1970 and April 21, 1970, for the preparation of Totacillin (Ampicillin Trihydrate) for Oral Suspension.

We have completed our review of this application with proposed labeling (insert). However, before the application may be approved, it will be necessary for you to submit twelve (12) copies of final printed labeling.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling or other action affecting the marketing of the drug may be required.

Sincerely yours,

Milton Eisler  
Division of Certification Services

CG:  
BD-240  
BD-240/ODJ  
BD-430/Lab.  
MEisler:hb

BEECHAM



PHARMACEUTICALS

DIVISION OF BEECHAM INC.

65 INDUSTRIAL SOUTH • CLIFTON, NEW JERSEY 07012 • Phone (201) 778-9000

*Approved by  
Dr. C. West  
201 5/1/70*

April 30, 1970

Dr. Alan E. Smith  
Director  
Division of Anti-infective Drugs  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, Maryland 20852

Dear Dr. Smith:

Subject: TOTACILLIN<sup>R</sup> (Ampicillin Trihydrate) Oral  
Suspension, 125 mg. and 250 mg.

We enclose with this letter final printed insert for  
TOTACILLIN<sup>R</sup> (Ampicillin Trihydrate) 125 mg. and 250 mg.  
Oral Suspension. This corresponds to the typed document  
which I placed in your hands on Friday, April 24, 1970.

We hope that this completes all necessary documentation  
required for final approval of this dosage form.

Yours sincerely,

C. West, Ph.D.  
Vice President  
Production

CW:rr

Enclosures (12)

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**Approval Package for:**

**APPLICATION NUMBER:**

**60-666 supplement**

Trade Name: Alpen for Oral Suspension  
125mg/5mL and 250mg/5mL

Generic Name: ampicillin trihydrate

Sponsor: Beecham Pharmaceuticals

Approval Date: July 14, 1970

# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:**

**60-666 supplement**

## CONTENTS

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Reviews / Information Included in this ANDA Review.

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Approval Letter(s)	X
Tentative Approval Letter(s)	
Final Printed Labeling	X
CSO Labeling Review(s)	
Medical Officer Review(s)	
Chemistry Review(s)	
Microbiology Review(s)	
Bioequivalence Review(s)	
Administrative Document(s)	
Correspondence	

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**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**APPROVAL LETTER**

BEECHAM



PHARMACEUTICALS

DIVISION OF BEECHAM INC.

101 POSSUMTOWN ROAD • PISCATAWAY, NEW JERSEY 08854 • Phone (201) 469-5200

A-6

1. Harrison  
2. Powers

June 29, 1970

Date Approved

7/14/70

Dr. John Harrison  
Food and Drug Administration  
Department of Health, Education,  
and Welfare  
560 Fishers Lane  
Rockville, Maryland 20852

Account No.

Signed

For the

Department

*John D. Harrison*  
Food and Drugs  
Administration and  
Welfare

Re: 60-666  
146a.118

3026

Dear Mr. Harrison:

We are hereby transmitting in triplicate, final labeling for the Alpen (Ampicillin Trihydrate) Oral Suspension, 125 mg./5 cc and 250 mg./5 cc.

This final labeling is for product to be manufactured by Beecham Pharmaceuticals in accordance with our Form 6 submitted to the Administration on November 3, 1969. This Lederle Alpen labeling is in strict accordance with our own brand Totacillin Oral Suspension submitted to the Administration on April 30, 1970 and approved on May 7, 1970.

It is our intention to manufacture the Alpen Oral Suspension for Lederle Laboratories and ship the finished product to Lederle after Certification.

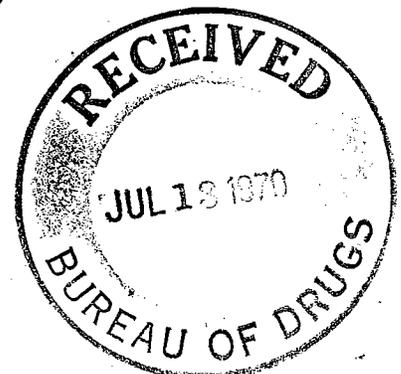
Enclosed herein are samples for the 80 cc trade package and the 5 cc sample package.

We trust that everything herein contained is in order and we would appreciate the Administration's action as soon as possible.

Yours sincerely,

*C. V. Rockoff*  
C. V. Rockoff  
Technical Manager

CVR/cag  
Enclosures



**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**FINAL PRINTED LABELING**

Lederle

3841-43

# Alpen<sup>\*</sup> Ampicillin Trihydrate for Oral Suspension

equivalent to 4.0 Gm. Ampicillin

**Cherry Flavored**

When reconstituted each 5 cc will contain

**250 mg.** Ampicillin

**CAUTION:** Federal law prohibits  
dispensing without prescription

**80 cc.** (when reconstituted)

Directions for Mixing  
Prior to Dispensing:  
Add 53 cc. of water to the  
bottle and shake vigorously.  
Each 5 cc contains:  
Ampicillin trihydrate  
equivalent to 250 mg Ampicillin

USUAL DOSAGE:

Children:

50-100 mg./kg./day

in divided doses

every 6-8 hours.

Adults:

250-500 mg every 6 hours.

**IMPORTANT:**

Read accompanying literature

for indications, dosage

and precautions.

\*© 1972, 458 of Mir.

Distributed by

**LEDERLE LABORATORIES**

**DIVISION**

American Cyanamid Company

Pearl River, N.Y. 10965

**KEEP TIGHTLY CLOSED  
SHAKE WELL BEFORE USING**

When stored at room temperature discard unused portion after 7 days;  
when stored under refrigeration discard unused portion after 14 days.  
Control No. Date Reconstituted

Exp. Date

**Lederle**

5-3840-43

# Alpen<sup>\*</sup>

## Ampicillin Trihydrate

for  
**Oral Suspension**

equivalent to 2.0 Gm. Ampicillin

**Cherry Flavored**

When reconstituted each 5 cc will contain

**125 mg.** Ampicillin

CAUTION: Federal law prohibits  
dispensing without prescription

**80 cc.** (when reconstituted)

Exp. Date

**KEEP TIGHTLY CLOSED  
SHAKE WELL BEFORE USING**

When stored at room temperature discard unused portion after 7 days;  
when stored under refrigeration discard unused portion after 14 days.  
Control No. \_\_\_\_\_ Date Reconstituted \_\_\_\_\_

**Directions for Mixing**  
**Prior to Dispensing:**  
Add 53 cc. of water to the  
bottle and shake vigorously.  
Each 5 cc contains:  
Ampicillin trihydrate  
equivalent to 125 mg Ampicillin

**USUAL DOSAGE:**  
**Children:**  
50-100 mg./kg./day  
in divided doses  
every 6-8 hours.

**Adults:**  
250-500 mg every 6 hours.

**IMPORTANT:**  
Read accompanying literature  
for indications, dosage  
and precautions.

\* © 872,458 of Mfr.

Distributed by  
**LEDERLE LABORATORIES**  
**DIVISION**  
American Cyanamid Company  
Pearl River, N.Y. 10965

**ALPEN\***  
**AMPICILLIN TRIHYDRATE**  
**FOR**  
**ORAL SUSPENSION**  
**125 mg./5 cc.**  
**and**  
**250 mg./5 cc.**

**DESCRIPTION**

ALPEN *ampicillin trihydrate* is derived from the penicillin nucleus, 6-amino-penicillanic acid (6-APA). Chemically it is D (-)  $\alpha$ -amino-benzylpenicillin.

**ACTIONS**

**MICROBIOLOGY:**

Ampicillin Trihydrate is similar to benzyl penicillin in its bacterial action against sensitive organisms during the stage of active multiplication. It acts through the inhibition of biosynthesis of cell wall mucopeptide. Ampicillin Trihydrate differs in *in vitro* spectrum from benzylpenicillin in the Gram negative spectrum. It exerts high *in vitro* activity against many strains of: *Hemophilus influenzae*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Neisseria catarrhalis*, *Escherichia coli*, *Proteus mirabilis*, *Bacteroides funduliformis*, *Salmonellae*, *Shigellae*.

*In vitro* studies have also demonstrated the sensitivity of many strains of the following Gram positive bacteria: alpha- and beta-hemolytic streptococci, *Diplococcus pneumoniae*; non-penicillinase producing staphylococci, *Bacillus anthracis*, and most strains of enterococci and clostridia. Ampicillin generally provides less *in vitro* activity than penicillin-G against Gram positive bacteria. Because it does not resist destruction by penicillinase it is not effective against penicillinase producing bacteria, particularly resistant staphylococci. All strains of *Pseudomonas* and most strains of *Klebsiella* and *Aerobacter* are resistant.

**PHARMACOLOGY:**

ALPEN *ampicillin trihydrate* is acid stable and therefore well absorbed. Food, however, retards absorption. Blood serum levels of approximately 2 mcg./ml. are attained within 1-2 hours following a 250 mg. oral dose given to fasting adults. Detectable amounts persist for about 6 hours. Ampicillin Trihydrate diffuses readily into all body tissues and fluids with the exception of brain and spinal fluid except when meninges are inflamed. Higher serum levels are obtained following I.M. injection. Most of the ampicillin is excreted unchanged in the urine and this excretion can be delayed by concurrent administration of probenecid. The active form appears in the bile in higher concentrations than found in the serum. Ampicillin Trihydrate is least serum bound of all the penicillins, averaging about 20% compared to approximately 60%-90% for other penicillins.

**INDICATIONS**

ALPEN *ampicillin trihydrate* is indicated in the treatment of infections due to susceptible strains of the following:

*Gram Negative Organisms - Shigellae, Salmonellae (including S. typhosa), H. influenzae, E. coli, P. mirabilis, N. gonorrhoeae and N. meningitidis.*

*Gram Positive Organisms - Streptococci, D. pneumoniae, and non-penicillinase producing staphylococci.*

Because of its wide spectrum and bactericidal action, it may be useful in instituting therapy; however, bacteriological studies to determine the causative organisms and their sensitivity to ampicillin should be performed.

Indicated surgical procedures should be performed.

**CONTRAINDICATIONS**

The use of this drug is contraindicated in individuals with a history of an allergic reaction to any of the penicillins.

**WARNINGS**

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL THERAPY IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. THESE REACTIONS ARE MORE APT TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR HYPERSENSITIVITY REACTIONS TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE THERAPY WITH A PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, THE DRUG SHOULD BE DISCONTINUED AND THE PATIENT TREATED WITH THE USUAL AGENTS, e.g., PRESSOR AMINES, ANTIHISTAMINES, AND CORTICOSTEROIDS.

**USAGE IN PREGNANCY:**

Safety for use in pregnancy has not been established.

**PRECAUTIONS**

As with any antibiotic preparation, constant observations for signs of overgrowth of nonsusceptible organisms, including fungi, is essential. Should superinfection occur (usually involving *Aerobacter*, *Pseudomonas*, or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.

As with any potent agent, it is advisable to check periodically for organ system dysfunction during prolonged therapy; this includes renal, hepatic, and hematopoietic systems. This is particularly important in premature, neonates and other infants.

**ADVERSE REACTIONS**

As with other penicillins, it may be expected that untoward reactions will be essentially limited to sensitivity phenomena. They are more likely to occur in individuals who have previously demonstrated hypersensitivity to penicillins and in those with a history of allergy, asthma, hay fever, or urticaria.

The following adverse reactions have been reported as associated with the use of ampicillin:

*Gastrointestinal, Glossitis, Stomatitis, Black "hairy" tongue, nausea, vomiting, diarrhea.*

(These reactions are usually associated with oral dosage forms).

*Hypersensitivity reactions, skin rashes, urticaria and erythema multiforme have been reported frequently. A few cases of exfoliative dermatitis have been reported. Anaphylaxis is the most serious reaction experienced and has usually been associated with the parenteral dosage form.*

**NOTE:**

Urticaria, other skin rashes, and serum sickness-like reactions may be controlled with antihistamines, and if necessary, systemic corticosteroids. Whenever such reactions occur, ampicillin should be discontinued, unless, in the opinion of the physician, the condition being treated is life threatening and amenable only to ampicillin therapy. Serious anaphylactic reactions require the immediate use of epinephrine, oxygen, and intravenous steroids.

**LIVER** - A moderate rise in serum glutamic oxaloacetic transaminase (SGOT) has been noted, particularly in infants, but the significance of this finding is unknown.

**HEMIC AND LYMPHATIC SYSTEMS**—Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leucopenia, and agranulocytosis have been reported during therapy with the penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be sensitivity reactions.

**DOSAGE**

*Infections of the ear, nose, throat, and lower respiratory tract due to streptococci, pneumococci, and non-penicillinase producing staphylococci; and also those infections of the upper and lower respiratory tract due to H. influenzae.*

Adults: 250 mg. every 6 hours.

Children: 50 mg/kg./day in divided doses every 6 or 8 hours.

*Infections of the genitourinary tract caused by sensitive Gram negative and Gram positive bacteria.*

Adults: 500 mg. every 6 hours. Larger doses may be required for severe infections.

Children: 100 mg./kg./day in divided doses every 6 hours.

*Urethritis due to N. gonorrhoeae.*

Adult Males: 500 mg. every 8 hours.

*Cases of gonorrhea with a suspected lesion of syphilis should have dark-field examinations before receiving ampicillin, and monthly serological tests for a minimum of 4 months.*

Infections of the gastrointestinal tract.

Adults: 500 mg. every 6 hours.

Children: 100 mg./kg./day in divided doses every 6 hours.

Larger doses may be required for stubborn or severe infections. The children's dosage is intended for individuals whose weight will not cause a dosage to be calculated greater than that recommended for adults. Children weighing more than 20 kg. should be dosed according to the adult recommendations.

It should be recognized that in the treatment of chronic urinary tract and intestinal infection, frequent bacteriological and clinical appraisal are necessary. Smaller doses than those recommended above should not be used. Even higher doses may be needed at times. In stubborn infections, therapy may be required for several weeks. It may be necessary to continue clinical and/or bacteriological follow-up for several months after-cessation of therapy.

Treatment should be continued for a minimum of 48 to 72 hours beyond the time that the patient becomes asymptomatic or evidence of bacterial eradication has been obtained. It is recommended that there be at least 10 days' treatment for any infection caused by hemolytic streptococci, to help prevent the occurrence of acute rheumatic fever or glomerulonephritis.

**DIRECTIONS FOR MIXING ORAL SUSPENSION**

Prepare either strength suspension at time of dispensing as follows: Add 53 cc. of water to the 80 cc. package. Shake vigorously. This will provide 80 cc. of suspension. Each teaspoonful (5 cc.) will contain 125 mg. or 250 mg. ampicillin. The reconstituted suspension is stable for 7 days at room temperature and 14 days under refrigeration.

**SUPPLY**

ALPEN ampicillin trihydrate for Oral Suspension. Each 5 cc. of reconstituted suspension contains ampicillin trihydrate equivalent to 125 mg. or 250 mg. ampicillin.

125 mg./5 cc.  
Product No. 3840-43  
80 cc. bottle

250 mg./5 cc.  
Product No. 3841-43  
80 cc. bottle



**LEDERLE LABORATORIES DIVISION**

**American Cyanamid Company, Pearl River, N.Y. 10965**

**KEEP BOTTLE  
TIGHTLY CLOSED**  
Discard after 7 days  
when stored at  
room temperature  
or low temperature  
under refrigeration.  
Control No.

Exp. Date

**1 DOSE** (when reconstituted)  
**SAMPLE NOT TO BE SOLD**  
**ALPEN\*** Cherry  
AMPICILLIN TRIHYDRATE Flavored  
for ORAL SUSPENSION  
Equivalent to 250 mg Ampicillin per dose  
CAUTION: Federal law prohibits  
dispensing without prescription.  
\*© 872,458 of Mfr.  
Distributed by  
**LEDERLE LABORATORIES DIVISION**  
American Cyanamid Company  
Pearl River, N.Y. 10965 1D1

389131  
When reconstituting, add sufficient water to fill reading, add sufficient amount of water to fill reading, allowing space for vigorous shaking. **USUAL DOSE:** Children: 50 mg/7.5 ml, 100 mg/15 ml, 250 mg/37.5 ml, 500 mg/75 ml, 750 mg/112.5 ml, 1000 mg/150 ml, 1500 mg/225 ml, 2000 mg/300 ml. **ADULT DOSE:** 250 mg/37.5 ml, 500 mg/75 ml, 750 mg/112.5 ml, 1000 mg/150 ml, 1500 mg/225 ml, 2000 mg/300 ml. **INDICATIONS:** See accompanying descriptive literature completely.

**KEEP BOTTLE  
TIGHT, CLOSED**  
Discard after 14 days  
when stored at  
room temperature  
or 14 days if stored  
under refrigeration.  
Control No.

Exp. Date

**1 DOSE** (when reconstituted)  
**SAMPLE NOT TO BE SOLD**  
**ALPEN\*** Cherry Flavored  
**AMPICILLIN TRIHYDRATE**  
for ORAL SUSPENSION  
Equivalent to 125 mg Ampicillin per dose  
**CAUTION:** Federal law prohibits  
dispensing without prescription.  
\*© 872,458 of Mfr.  
Distributed by  
**LEDERLE LABORATORIES DIVISION**  
American Cyanamid Company  
Pearl River, N.Y. 10965 101

**3840-31**  
When dispensing add sufficient water to one dose bottle to reach volume indicated on label. Shake to suspend the contents.  
100 mg./5ML./5oz. (500 mg./5oz.)  
100 mg./5oz. Admin. 250-500 mg. every 6 hours.  
Read the accompanying descriptive literature completely.

**ALPEN\***

**AMPICILLIN TRIHYDRATE**

**for ORAL SUSPENSION 250 mg.**

Equivalent to 250 mg Ampicillin per Dose  
CHERRY FLAVORED

3 x 1 Dose when reconstituted

Usual Dosage:

Children: 50 - 100 mg/kg/day in divided doses every 6-8 hours.

Adults: 250 - 500 mg every 6 hours. IMPORTANT: Read the

accompanying descriptive literature completely.

CAUTION: Federal law prohibits dispensing without prescription.

Distributed by

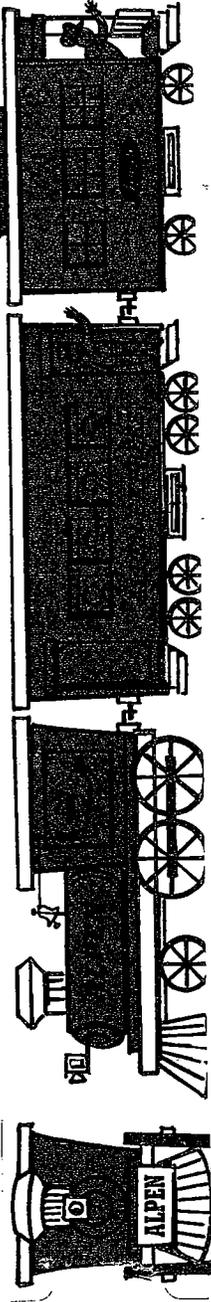
**LEDERLE LABORATORIES DIVISION**

American Cyanamid Company, Pearl River, N.Y. 10965



\* © 872,458 of Mfr.

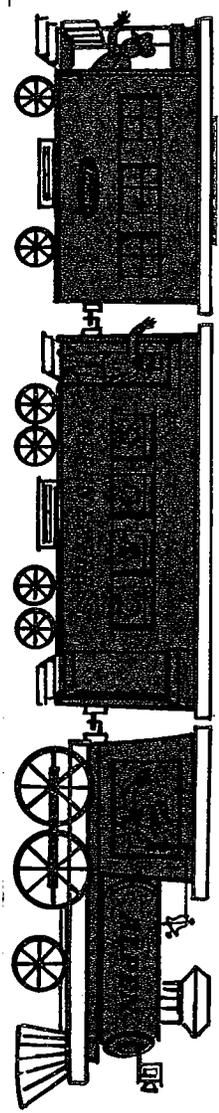
2431



**KEEP BOTTLES TIGHTLY CLOSED**

When dispensing add sufficient water to fill one dose bottle to neck allowing space for vigorous shaking to suspend the contents. Discard contents after 7 days when stored at room temperature or 14 days when refrigerated.

**SAMPLE - NOT TO BE SOLD** 3841-028 1D1



Control No.

Exp. Date

2430

**ALPEN<sup>®</sup>**  
**AMPICILLIN TRIHYDRATE**  
**for ORAL SUSPENSION 125 mg.**

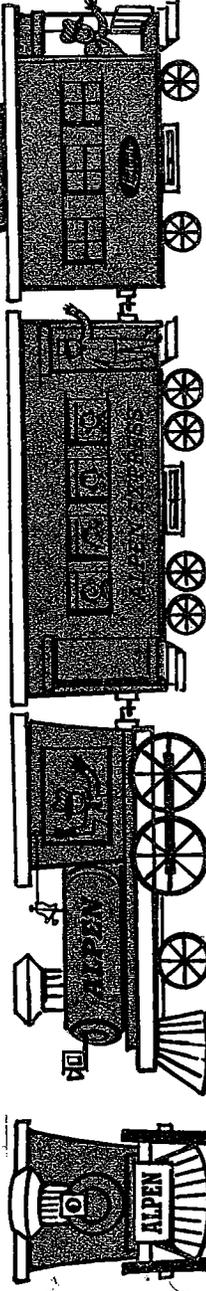
Equivalent to 125 mg Ampicillin per Dose  
CHERRY FLAVORED

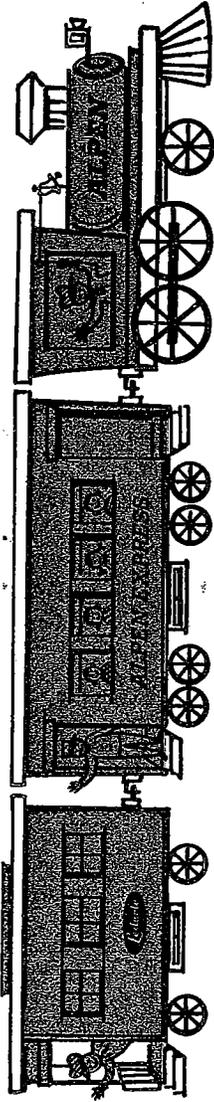
**3 x 1 Dose when reconstituted**  
Usual Dosage:  
Children: 50 - 100 mg/kg/day in divided doses every 6-8 hours.  
Adults: 250 - 500 mg every 6 hours. **IMPORTANT:** Read the  
accompanying descriptive literature completely before use.  
**CAUTION:** Federal law prohibits dispensing without prescription.



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**LEDERLE LABORATORIES DIVISION**  
American Cyanamid Company, Pearl River, N.Y. 10965

© 872,458 of Mfr.





Control No.

Exp. Date

**KEEP BOTTLES TIGHTLY CLOSED**  
 When dispensing add sufficient water to fill one dose bottle to neck, allowing space for vigorous shaking to suspend the contents. Discard contents after 14 days when stored at room temperature or 14 days when refrigerated.  
**SAMPLE - NOT TO BE SOLD**

3840-028

1D1

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**Approval Package for:**

**APPLICATION NUMBER:**

**60-666 supplement**

Trade Name: Totacillin for Oral Suspension  
125mg/5mL and 250mg/5mL

Generic Name: ampicillin trihydrate

Sponsor: Beecham Pharmaceuticals

Approval Date: August 25, 1970

# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:**

**60-666 supplement**

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Medical Officer Review(s)	
Chemistry Review(s)	
Microbiology Review(s)	
Bioequivalence Review(s)	
Administrative Document(s)	
Correspondence	

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**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**APPROVAL LETTER**

BEECHAM



PHARMACEUTICALS

DIVISION OF BEECHAM INC.

101 POSSUMTOWN ROAD • PISCATAWAY, NEW JERSEY 08854 • Phone (201) 469-5200

A-6

~~Handwritten scribble~~

①

For use of Food and Drug Administration)  
 Date approved 8-25-70  
 Control No. \_\_\_\_\_  
 Signed William T. Robinson  
 For the Commissioner of Food and Drugs  
 Food and Drug Administration  
 Department of Health, Education, and Welfare

OK to sign out  
COP 8/25/70

August 17, 1970

03613

Mr. John Harrison  
Food and Drug Administration (DHEW)  
5600 Fishers Lane  
Rockville, Maryland 20852

Ref: #60-666-146a.118

Dear Mr. Harrison:

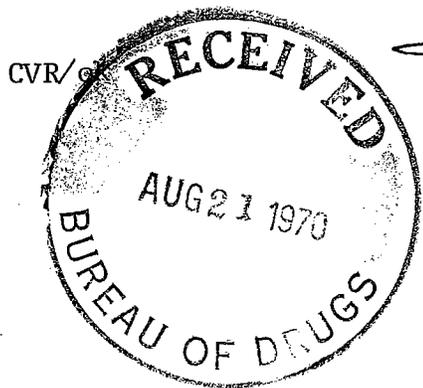
We are hereby transmitting in triplicate to you cartons and labels for a 5 cc sample of the Totacillin (ampicillin trihydrate) oral suspension 125 mg./5 cc and 250 mg./5cc.

Please note that three bottles will be in each carton and that the expiration date and control number will be viewed through the hole in the carton.

We would appreciate the Administration's speedy action upon this request for approval.

Sincerely,

*C. V. Rockoff*  
C. V. Rockoff

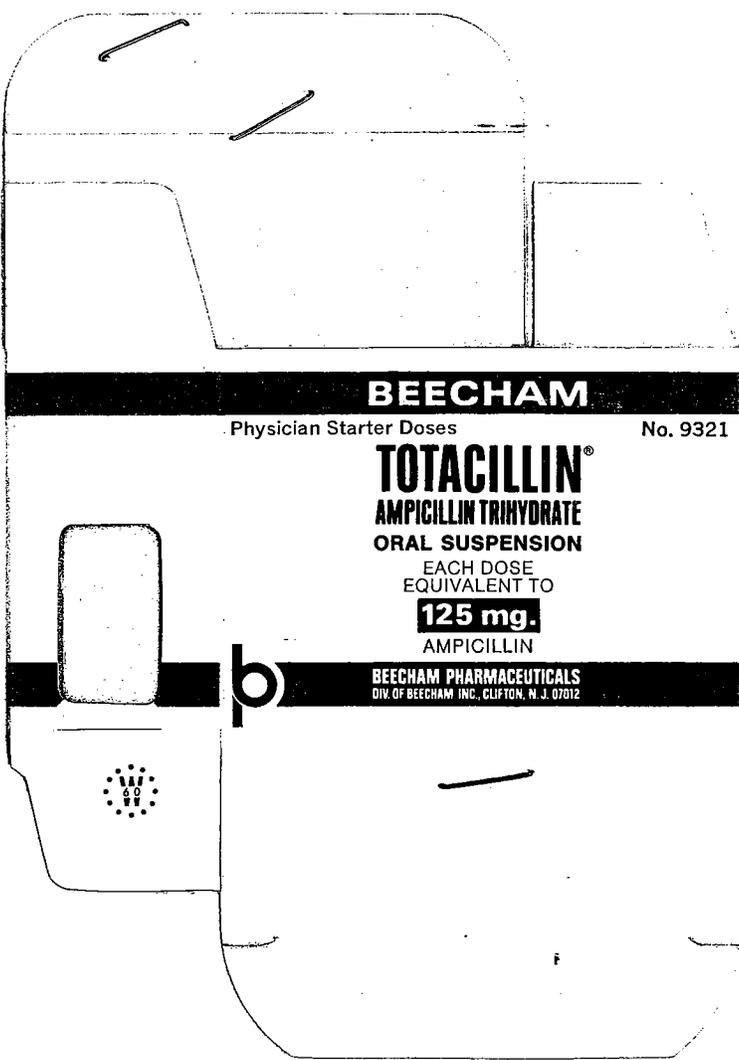


**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**FINAL PRINTED LABELING**



**BEECHAM**

Physician Starter Doses

No. 9321

**TOTACILLIN<sup>®</sup>**  
**AMPICILLIN TRIHYDRATE**  
**ORAL SUSPENSION**  
 EACH DOSE  
 EQUIVALENT TO  
**125 mg.**  
**AMPICILLIN**

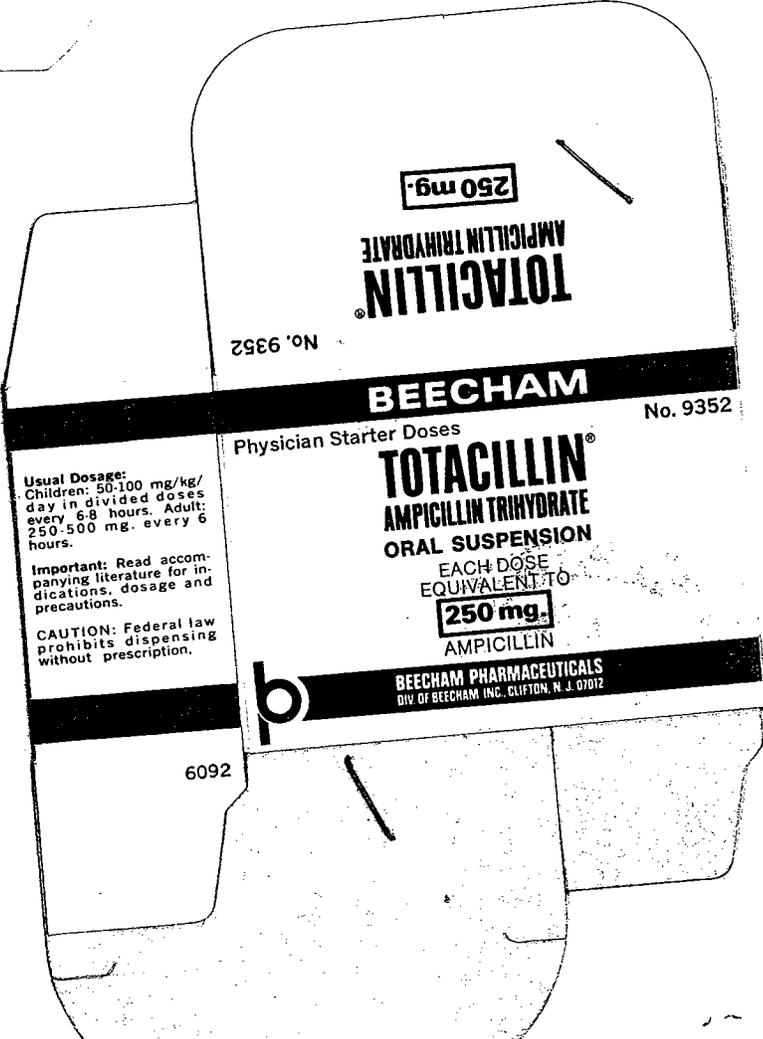
**BEECHAM PHARMACEUTICALS**  
 DIV. OF BEECHAM INC., CLIFTON, N. J. 07012



Exp. Date.  
 Control No. 6033

**BEECHAM**  
 1 Dose No. 9321  
**TOTACILLIN<sup>®</sup>**  
**AMPICILLIN TRIHYDRATE**  
 ORAL SUSPENSION  
 EQUIVALENT TO  
**125 mg.**  
**AMPICILLIN**  
 BEECHAM PHARMACEUTICALS  
 DIV. OF BEECHAM INC., CLIFTON, N. J. 07012

NDC 319-9321-05  
 CAUTION: Federal law prohibits dispensing without prescription.  
**PHYSICIAN STARTER DOSE**  
 Directions for mixing: Add 3.2cc water and shake vigorously. The resulting suspension contains ampicillin trihydrate equivalent to 125 mg. ampicillin.  
**Usual Dosage:**  
 Children: 50-100mg/kg/day in divided doses every 6-8 hours; Adults: 250-500 mg. every 6 hours.  
**IMPORTANT:** Read accompanying literature for indications, dosage and precautions.



**250 mg.**

**TOTACILLIN<sup>®</sup>**  
**AMPICILLIN TRIHYDRATE**

No. 9352

**BEECHAM**

No. 9352

Physician Starter Doses

**TOTACILLIN<sup>®</sup>**  
**AMPICILLIN TRIHYDRATE**  
**ORAL SUSPENSION**  
 EACH DOSE  
 EQUIVALENT TO  
**250 mg.**  
**AMPICILLIN**

**BEECHAM PHARMACEUTICALS**  
 DIV. OF BEECHAM INC., CLIFTON, N. J. 07012

**Usual Dosage:**  
 Children: 50-100 mg/kg/day in divided doses every 6-8 hours. Adult: 250-500 mg. every 6 hours.  
**Important:** Read accompanying literature for indications, dosage and precautions.  
**CAUTION:** Federal law prohibits dispensing without prescription.

6092

Exp. Date.  
 Control No. 6034

**BEECHAM**  
 1 Dose No. 9352  
**TOTACILLIN<sup>®</sup>**  
**AMPICILLIN TRIHYDRATE**  
 ORAL SUSPENSION  
 EQUIVALENT TO  
**250 mg.**  
**AMPICILLIN**  
 BEECHAM PHARMACEUTICALS  
 DIV. OF BEECHAM INC., CLIFTON, N. J. 07012

NDC 319-9352-05  
 CAUTION: Federal law prohibits dispensing without prescription.  
**PHYSICIAN STARTER DOSE**  
 Directions for mixing: Add 3.2cc water and shake vigorously. The resulting suspension contains ampicillin trihydrate equivalent to 250 mg. ampicillin.  
**Usual Dosage:**  
 Children: 50-100mg/kg/day in divided doses every 6-8 hours; Adults: 250-500 mg. every 6 hours.  
**IMPORTANT:** Read accompanying literature for indications, dosage and precautions.



**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**Approval Package for:**

**APPLICATION NUMBER:**

**60-666 supplement**

Trade Name: Totacillin for Oral Suspension  
125mg/5mL and 250mg/5mL

Generic Name: ampicillin trihydrate

Sponsor: Beecham Pharmaceuticals

Approval Date: October 14, 1970

# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:**

**60-666 supplement**

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Correspondence	

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**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**APPROVAL LETTER**

①

*Fowers*

**BEECHAM **p** PHARMACEUTICALS**

DIVISION OF BEECHAM INC.

65 INDUSTRIAL SOUTH • CLIFTON, NEW JERSEY 07012 • Phone (201) 778-9000

September 30, 1970

*OK to sign out  
JOP 10/13/70*

Mr. John Harrison  
Food and Drug Administration  
Certification Services Branch  
5600 Fishers Lane  
Rockville, Maryland 20852

(For use of Food and Drug Administration)
Date approved <u>10/14/70</u>
Account No. _____
Signed <u>John R. Garrison</u>
For the Commissioner of Food and Drugs BD-145 Food and Drug Administration Department of Health, Education, and Welfare

Re: #60-666 (146a.118)

Dear Mr. Harrison:

We are transmitting herewith, in triplicate, a supplement to Beecham Pharmaceuticals' approved Form 6 (#60-666) for Totacillin (ampicillin trihydrate) for Oral Suspension.

This supplement provides for:

a) revised labeling: Package insert — (Aug. 1970), which is in compliance with your letter of July 10, 1970 pertaining to Hypersensitivity Reactions;

b) packaging change: the unit cartons for all dosages will be eliminated, package inserts will be fastened to the containers by a plastic strap.

We trust that the Administration will find this information in order. Your early attention to the above would be greatly appreciated.

Sincerely yours,

*George Vadnai*

George Vadnai  
Regulatory Affairs Manager

GV:ms

01239



**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**FINAL PRINTED LABELING**

**BEECHAM****TOTACILLIN®****Ampicillin Trihydrate**for  
**Oral Suspension**

125 mg./5 cc.

and

250 mg./5 cc.

**Description**

TOTACILLIN (Ampicillin Trihydrate) is derived from the penicillin nucleus, 6-aminopenicillanic acid (6-APA), isolated by Beecham. Chemically it is D (-) *a*-aminobenzyl penicillin.

**Actions****MICROBIOLOGY:**

TOTACILLIN (Ampicillin Trihydrate) is similar to benzyl penicillin in its bactericidal action against sensitive organisms during the stage of active multiplication. It acts through the inhibition of biosynthesis of cell wall mucopeptide. TOTACILLIN (Ampicillin Trihydrate) differs in *in vitro* spectrum from benzyl penicillin in the Gram negative spectrum. It exerts high *in vitro* activity against many strains of *Hemophilus influenzae*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, and *Neisseria catarrhalis*, *Escherichia coli*, *Proteus mirabilis*, *Bacteroides funduliformis*, *Salmonellae* and *Shigellae*.

*In vitro* studies have also demonstrated the sensitivity of many strains of the following Gram positive bacteria: alpha- and beta-hemolytic streptococci, *Diplococcus pneumoniae*, non-penicillinase producing staphylococci, *Bacillus anthracis*, and most strains of enterococci and clostridia. Ampicillin generally provides less *in vitro* activity than penicillin-G against Gram positive bacteria. Because it does not resist destruction by penicillinase it is not effective against penicillinase producing bacteria, particularly resistant staphylococci. All strains of *Pseudomonas* and most strains of *Klebsiella* and *Aerobacter* are resistant.

**PHARMACOLOGY:**

TOTACILLIN (Ampicillin Trihydrate) is acid stable and therefore well absorbed. Food, however, retards absorption. Blood serum levels of approximately 2 mcg./ml. are attained within 1-2 hours following a 250 mg. oral dose given to fasting adults. Detectable amounts persist about 6 hours. TOTACILLIN (Ampicillin Trihydrate) diffuses freely into all body tissues and fluids with the exception of brain and spinal fluid except when meninges are inflamed. Higher serum levels are obtained following I.M. injection. Most of the ampicillin is excreted unchanged in the urine and this excretion can be delayed by concurrent administration of probenecid. The active form appears in the bile in higher concentrations than found in the serum. TOTACILLIN (Ampicillin Trihydrate) is least serum bound of all the penicillins, averaging about 20% compared to approximately 60%-90% for other penicillins.

**Indications**

TOTACILLIN (Ampicillin Trihydrate) is indicated in the treatment of infections due to susceptible strains of the following:

*Gram Negative Organisms*—*Shigellae*, *Salmonellae* (including *S. typhosa*), *H. influenzae*, *E. coli* and *P. mirabilis*, *N. gonorrhoeae*, and *N. meningitidis*.

*Gram Positive Organisms*—Streptococci, *D. pneumoniae*, and non-penicillinase producing staphylococci.

Because of its wide spectrum and bactericidal action, it may be useful in instituting therapy; however, bacteriological studies to determine the causative organisms and their sensitivity to ampicillin should be performed.

Indicated surgical procedures should be performed.

**Contraindications**

The use of this drug is contraindicated in individuals with a history of an allergic reaction to any of the penicillins.

**Warnings**

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL THERAPY IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. THESE REACTIONS ARE MORE APT TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR HYPERSENSITIVITY REACTIONS TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE TREATMENT WITH A PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, THE DRUG SHOULD BE DISCONTINUED AND THE PATIENT TREATED WITH THE USUAL AGENTS, e.g., PRESSOR AMINES, ANTIHISTAMINES, AND CORTICOSTEROIDS.

**USAGE IN PREGNANCY:**

Safety for use in pregnancy has not been established.

**Precautions**

As with any antibiotic preparation, constant observations for signs of overgrowth of nonsusceptible organisms, including fungi, is essential. Should superinfection occur (usually involving *Aerobacter*, *Pseudo-*

(continued on other side)

(continued from other side)

monas, or Candida), the drug should be discontinued and/or appropriate therapy instituted.

As with any potent agent, it is advisable to check periodically for organ system dysfunction during prolonged therapy; this includes renal, hepatic, and hematopoietic systems. This is particularly important in prematures, neonates and other infants.

#### Adverse Reactions

As with other penicillins, it may be expected that untoward reactions will be essentially limited to sensitivity phenomena. They are more likely to occur in individuals who have previously demonstrated hypersensitivity to penicillins and in those with a history of allergy, asthma, hay fever, or urticaria.

The following adverse reactions have been reported as associated with the use of ampicillin:

**Gastrointestinal**—Glossitis, Stomatitis, black "hairy" tongue, nausea, vomiting, and diarrhea. (These reactions are usually associated with oral dosage forms).

**Hypersensitivity reactions**—An erythematous maculopapular rash has been reported fairly frequently. Urticaria and erythema multiforme have been reported occasionally. A few cases of exfoliative dermatitis have been reported. Anaphylaxis is the most serious reaction experienced and has usually been associated with the parenteral dosage form. *Note:* Urticaria, other skin rashes, and serum sickness-like reactions may be controlled with antihistamines, and if necessary, systemic corticosteroids. Whenever such reactions occur, ampicillin should be discontinued, unless, in the opinion of the physician, the condition being treated is life threatening and amenable only to ampicillin therapy. Serious anaphylactic reactions require the immediate use of epinephrine, oxygen, and intravenous steroids.

#### LIVER—

A moderate rise in serum glutamic oxaloacetic transaminase (SGOT) has been noted, particularly in infants, but the significance of this finding is unknown.

#### HEMIC AND LYMPHATIC SYSTEMS—

Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leucopenia, and agranulocytosis have been reported during therapy with the penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be sensitivity reactions.

#### Dosage

*Infections of the ear, nose, throat, and lower respiratory tract* due to streptococci, pneumococci, and non-penicillinase producing staphylococci; and also those infections of the upper and lower respiratory tract due to *H. influenzae*.

*Adults:* 250 mg. every 6 hours.

*Children:* 50 mg./kg./day in divided doses every 6 or 8 hours.

*Infections of the genitourinary tract caused by sensitive Gram negative and Gram positive bacteria.*

*Adults:* 500 mg. every 6 hours. Larger doses may be required for severe infections.

*Children:* 100 mg./kg./day in divided doses every 6 hours.

*Urethritis due to N. gonorrhoeae.*

*Adult Males:* 500 mg. every 8 hours.

*Cases of gonorrhea with a suspected lesion of syphilis should have dark-field examinations before receiving ampicillin, and monthly serological tests for a minimum of 4 months.*

*Infections of the gastrointestinal tract.*

*Adults:* 500 mg. every 6 hours.

*Children:* 100 mg./kg./day in divided doses every 6 hours.

Larger doses may be required for stubborn or severe infections. The children's dosage is intended for individuals whose weight will not cause a dosage to be calculated greater than that recommended for adults. Children weighing more than 20 kg. should be dosed according to the adult recommendations.

It should be recognized that in the treatment of chronic urinary tract and intestinal infections, frequent bacteriological and clinical appraisal are necessary. Smaller doses than those recommended above should not be used. Even higher doses may be needed at times. In stubborn infections, therapy may be required for several weeks. It may be necessary to continue clinical and/or bacteriological follow-up for several months after cessation of therapy.

Treatment should be continued for a minimum of 48 to 72 hours beyond the time that the patient becomes asymptomatic or evidence of bacterial eradication has been obtained. It is recommended that there be at least 10 days' treatment for any infection caused by hemolytic streptococci, to help prevent the occurrence of acute rheumatic fever or glomerulonephritis.

#### Directions for Mixing Oral Suspension

Prepare suspension at time of dispensing as follows: Add 53 cc. of water to the 80 cc. package and 100 cc. of water to the 150 cc. package. Shake vigorously. This will provide 80 and 150 cc. of suspension, respectively. Each teaspoonful (5 cc.) will contain 125 mg. or 250 mg. TOTACILLIN (Ampicillin Trihydrate). The reconstituted suspension is stable for 7 days at room temperature and 14 days in refrigeration.

#### Supply

TOTACILLIN (Ampicillin Trihydrate) for Oral Suspension. Each 5 cc. of reconstituted suspension contains ampicillin trihydrate equivalent to 125 mg. or 250 mg. ampicillin.

125 mg./5 cc.

250 mg./5 cc.

List No. 9312..... 80 cc. bottle

List No. 9325..... 80 cc. bottle

List No. 9412..... 150 cc. bottle

List No. 9425..... 150 cc. bottle

BEECHAM PHARMACEUTICALS  
Division of Beecham Inc.  
Clifton, New Jersey 07012

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**Approval Package for:**

**APPLICATION NUMBER:**

**60-666 supplement**

Trade Name: Totacillin for Oral Suspension  
125mg/5mL and 250mg/5mL

Generic Name: ampicillin trihydrate

Sponsor: Beecham-Massengill

Approval Date: February 17, 1972

# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:**

**60-666 supplement**

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**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**APPROVAL LETTER**

①

A-6  
~~WERS~~

# Beecham-Massengill Pharmaceuticals

DIV. OF BEECHAM INC. CLIFTON, NEW JERSEY

65 INDUSTRIAL SOUTH  
CLIFTON, NEW JERSEY 07012

CABLE ADDRESS "BEECHPROD"  
TELEX 133471

PHONES NEW JERSEY 201-778-9000  
TENNESSEE 615-764-5141

*OK to sign out  
2/9/72*

February 11, 1972

Food and Drug Administration  
Bureau of Drugs  
Div. of Anti-Infective Drug Products  
Certifiable Drugs Review Unit (BD-145)  
5600 Fishers Lane  
Rockville, Maryland 20852

(For use of Food and Drug Administration)	
Date approved	<u>2-17-72</u>
Account No.	
Signed	<u>William T. Roman</u>
For the Commissioner of Food and Drugs Food and Drug Administration Department of Health, Education, and Welfare	

Re: #60-666 (146a.118) Supplement

Gentlemen:

Pursuant to Sections 140.14 and 130.9 of the Regulations, we hereby submit, in triplicate, a supplement to Beecham-Massengill Pharmaceuticals' approved Form 6 Application, covering Totacillin® (Ampicillin trihydrate) for Oral Suspension.

This supplement provides for new labeling, reflecting the change in the company name (re: Letter of June 30, 1971) and the new product codes. The new labeling will be in use on or about February 15, 1972.

Sincerely yours,

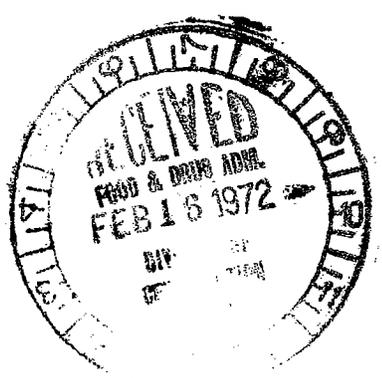
BEECHAM-MASSENGILL PHARMACEUTICALS

*George Vadnai*

George Vadnai  
Manager, Governmental Affairs

GSV:dmm

Enclosures



4387

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**FINAL PRINTED LABELING**

**KEEP TIGHTLY CLOSED • SHAKE WELL BEFORE USING**  
 When stored at room temperature discard unused portion after 7 days;  
 when stored under refrigeration discard unused portion after 14 days.  
 Control No. \_\_\_\_\_  
 Exp. Date \_\_\_\_\_  
 Tear along perforation

**IMPORTANT:** Read accompanying literature for indications, dosage and precautions.  
**CAUTION:** Federal law prohibits dispensing without prescription.

NDC 29 6630 21  
**BMP**  
**TOTACILLIN®**  
 Ampicillin Trihydrate  
 for Oral Suspension

Equivalent to  
 4.0 Gm. Ampicillin

When reconstituted  
 each 5 cc. will contain

**250 mg.**  
 Ampicillin

80 cc. (2 2/3 fl. oz.)

*Beecham-Massengill*  
 PHARMACEUTICALS  
 DIV. OF BEECHAM INC., BRISTOL, TENN. 37620

TOTACILLIN® is a Registered Trademark

Directions for Mixing  
 Add 53 cc. of water and shake vigorously. Each 5 cc. (1 teaspoonful) contains ampicillin trihydrate equivalent to 250 mg. ampicillin.

Usual dosage—  
 Children: 50-100 mg./kg./day in divided doses every 6-8 hours.  
 Adults: 250-500 mg. every 6 hours.

Made in U.S.A. 6312

**KEEP TIGHTLY CLOSED • SHAKE WELL BEFORE USING**  
 When stored at room temperature discard unused portion after 7 days;  
 when stored under refrigeration discard unused portion after 14 days.  
 Control No. \_\_\_\_\_  
 Exp. Date \_\_\_\_\_  
 Tear along perforation

**IMPORTANT:** Read accompanying literature for indications, dosage and precautions.  
**CAUTION:** Federal law prohibits dispensing without prescription.

NDC 29 6630 22  
**BMP**  
**TOTACILLIN®**  
 Ampicillin Trihydrate  
 for Oral Suspension

Equivalent to  
 7.50 Gm. Ampicillin

When reconstituted  
 each 5 cc. will contain

**250 mg.**  
 Ampicillin

150 cc. (5 fl. oz.)

*Beecham-Massengill*  
 PHARMACEUTICALS  
 DIV. OF BEECHAM INC., BRISTOL, TENN. 37620

TOTACILLIN® is a Registered Trademark

Directions for Mixing  
 Add 100 cc. of water and shake vigorously. Each 5 cc. (1 teaspoonful) contains ampicillin trihydrate equivalent to 250 mg. ampicillin.

Usual dosage—  
 Children: 50-100 mg./kg./day in divided doses every 6-8 hours.  
 Adults: 250-500 mg. every 6 hours.

Made in U.S.A. 6315

**KEEP TIGHTLY CLOSED • SHAKE WELL BEFORE USING**  
 When stored at room temperature discard unused portion after 7 days;  
 when stored under refrigeration discard unused portion after 14 days.  
 Control No. \_\_\_\_\_  
 Exp. Date \_\_\_\_\_  
 Tear along perforation

**IMPORTANT:** Read accompanying literature for indications, dosage and precautions.  
**CAUTION:** Federal law prohibits dispensing without prescription.

NDC 29 6625 21  
**BMP**  
**TOTACILLIN®**  
 Ampicillin Trihydrate  
 for Oral Suspension

Equivalent to  
 2.0 Gm. Ampicillin

When reconstituted  
 each 5 cc. will contain

**125 mg.**  
 Ampicillin

80 cc. (2 2/3 fl. oz.)

*Beecham-Massengill*  
 PHARMACEUTICALS  
 DIV. OF BEECHAM INC., BRISTOL, TENN. 37620

TOTACILLIN® is a Registered Trademark

Directions for Mixing  
 Add 53 cc. of water and shake vigorously. Each 5 cc. (1 teaspoonful) contains ampicillin trihydrate equivalent to 125 mg. ampicillin.

Usual dosage—  
 Children: 50-100 mg./kg./day in divided doses every 6-8 hours.  
 Adults: 250-500 mg. every 6 hours.

**KEEP TIGHTLY CLOSED • SHAKE WELL BEFORE USING**  
 When stored at room temperature discard unused portion after 7 days;  
 when stored under refrigeration discard unused portion after 14 days.  
 Control No. \_\_\_\_\_  
 Exp. Date \_\_\_\_\_  
 Tear along perforation

**IMPORTANT:** Read accompanying literature for indications, dosage and precautions.  
**CAUTION:** Federal law prohibits dispensing without prescription.

NDC 29 6625 22  
**BMP**  
**TOTACILLIN®**  
 Ampicillin Trihydrate  
 for Oral Suspension

Equivalent to  
 3.75 Gm. Ampicillin

When reconstituted  
 each 5 cc. will contain

**125 mg.**  
 Ampicillin

150 cc. (5 fl. oz.)

*Beecham-Massengill*  
 PHARMACEUTICALS  
 DIV. OF BEECHAM INC., BRISTOL, TENN. 37620

TOTACILLIN® is a Registered Trademark

Directions for Mixing  
 Add 100 cc. of water and shake vigorously. Each 5 cc. (1 teaspoonful) contains ampicillin trihydrate equivalent to 125 mg. ampicillin.

Usual dosage—  
 Children: 50-100 mg./kg./day in divided doses every 6-8 hours.  
 Adults: 250-500 mg. every 6 hours.

Made in U.S.A. 6309

Ampicillin

125 mg.

Each dose equivalent to

TOTACILLIN<sup>®</sup>  
Ampicillin Trihydrate  
for Oral Suspension

NDC 29 6625 01

NDC 29 6625 01

**TOTACILLIN<sup>®</sup>**  
Ampicillin Trihydrate  
for Oral Suspension

Each dose equivalent to

125 mg.

Ampicillin

3 Physician Starter Doses

*Beecham-Massengill*

PHARMACEUTICALS  
DIV. OF BEECHAM INC. BRISTOL, TENN. 37620

Usual Dosage:  
Children: 50-100 mg./  
kg./day in divided doses  
every 6-8 hours. Adult:  
250-500 mg. every 6  
hours.

**IMPORTANT:** Read  
accompanying literature  
for indications, dosage  
and precautions.

**CAUTION:** Federal law  
prohibits dispensing  
without prescription.

Made in U.S.A.

63028

Ampicillin

250 mg.

Each dose equivalent to

TOTACILLIN<sup>®</sup>  
Ampicillin Trihydrate  
for Oral Suspension

NDC 29 6630 01

NDC 29 6630 01

**TOTACILLIN<sup>®</sup>**  
Ampicillin Trihydrate  
for Oral Suspension

Each dose equivalent to

250 mg.

Ampicillin

3 Physician Starter Doses

*Beecham-Massengill*

PHARMACEUTICALS  
DIV. OF BEECHAM INC. BRISTOL, TENN.

Usual Dosage:  
Children: 50-100 mg./  
kg./day in divided doses  
every 6-8 hours. Adult:  
250-500 mg. every 6  
hours.

**IMPORTANT:** Read  
accompanying literature  
for indications, dosage  
and precautions.

**CAUTION:** Federal law  
prohibits dispensing  
without prescription.

Made in U.S.A.

6319S

NDC 29 6625 01

**BMP**  
**TOTACILLIN<sup>®</sup>**  
Ampicillin Trihydrate

for Oral Suspension

Each dose equivalent to

**125 mg.**

Ampicillin

**3 Physician Starter Doses**

TOTACILLIN<sup>®</sup> is a Registered Trademark

*Beecham-Massengill*

PHARMACEUTICALS  
DIV. OF BEECHAM INC. BRISTOL, TENN. 37620

ROBERTSON  
12345

NDC 29 6630 01

**BMP**  
**TOTACILLIN<sup>®</sup>**  
Ampicillin Trihydrate

for Oral Suspension

Each dose equivalent to

**250 mg.**

Ampicillin

**3 Physician Starter Doses**

TOTACILLIN<sup>®</sup> is a Registered Trademark

*Beecham-Massengill*

PHARMACEUTICALS  
DIV. OF BEECHAM INC. BRISTOL, TENN. 37620

ROBERTSON  
12345

Exp. Date  
Control No.  
Keep tightly closed  
Shake well before using

NDC 29 6630 01  
**TOTACILLIN**<sup>®</sup>  
Ampicillin Trihydrate  
for Oral Suspension  
Equivalent to  
250 mg.  
Ampicillin  
1 DOSE  
**Beecham-Massengill**  
Pharmaceuticals  
200 W. 42nd St., N.Y.C. 36, N.Y. 10018

**CAUTION:** Federal law prohibits dispensing without prescription.

**PHYSICIAN STARTER DOSE**  
Directions for mixing: Add 100 ml. of water to 3.3 cc. of suspension vigorously. The resulting suspension contains ampicillin trihydrate equivalent to 250 mg. ampicillin.

**Usual dosage:**  
Children: 50-100 mg./kg./day in divided doses every 6-8 hours. Adults: 250-500 mg. every 6 hours.

**IMPORTANT:** Read accompanying literature for indications, dosage and precautions.

Made in U.S.A.

63185

Exp. Date  
Control No.  
Keep tightly closed  
Shake well before using

NDC 29 6625 01  
**TOTACILLIN**<sup>®</sup>  
Ampicillin Trihydrate  
for Oral Suspension  
Equivalent to  
125 mg.  
Ampicillin  
1 DOSE  
**Beecham-Massengill**  
Pharmaceuticals  
200 W. 42nd St., N.Y.C. 36, N.Y. 10018

**CAUTION:** Federal law prohibits dispensing without prescription.

**PHYSICIAN STARTER DOSE**  
Directions for mixing: Add 2/3 teaspoonful of water to 1 cc. of suspension vigorously. The resulting suspension contains ampicillin trihydrate equivalent to 125 mg. ampicillin.

**Usual dosage:**  
Children: 50-100 mg./kg./day in divided doses every 6-8 hours. Adults: 250-500 mg. every 6 hours.

**IMPORTANT:** Read accompanying literature for indications, dosage and precautions.

Made in U.S.A.

51073

## TOTACILLIN® AMPICILLIN TRIHYDRATE for ORAL SUSPENSION 125 mg./5 cc. and 250 mg./5 cc.

### Description

TOTACILLIN (Ampicillin Trihydrate) is derived from the penicillin nucleus, 6-aminopenicillanic acid (6-APA), isolated by Beecham. Chemically it is D (-)  $\alpha$ -aminobenzyl penicillin.

### Actions

#### MICROBIOLOGY:

TOTACILLIN (Ampicillin Trihydrate) is similar to benzyl penicillin in its bactericidal action against sensitive organisms during the stage of active multiplication. It acts through the inhibition of biosynthesis of cell wall mucopeptide. TOTACILLIN (Ampicillin Trihydrate) differs in *in vitro* spectrum from benzyl penicillin in the Gram-negative spectrum. It exerts high *in vitro* activity against many strains of *Hemophilus influenzae*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, and *Neisseria catarrhalis*, *Escherichia coli*, *Proteus mirabilis*, *Bacteroides funduliformis*, *Salmonellae* and *Shigellae*.

*In vitro* studies have also demonstrated the sensitivity of many strains of the following Gram-positive bacteria: alpha- and beta-hemolytic streptococci, *Diplococcus pneumoniae*, non-penicillinase producing staphylococci, *Bacillus anthracis*, and most strains of enterococci and clostridia. Ampicillin generally provides less *in vitro* activity than penicillin-G against Gram-positive bacteria. Because it does not resist destruction by penicillinase, it is not effective against penicillinase producing bacteria, particularly resistant staphylococci. All strains of *Pseudomonas* and most strains of *Klebsiella* and *Aerobacter* are resistant.

#### PHARMACOLOGY:

TOTACILLIN (Ampicillin Trihydrate) is acid stable and therefore well absorbed. Food, however, retards absorption. Blood serum levels of approximately 2 mcg./ml. are attained within 1-2 hours following a 250 mg. oral dose given to fasting adults. Detectable amounts persist for about 6 hours. TOTACILLIN (Ampicillin Trihydrate) diffuses readily into all body tissues and fluids with the exception of brain and spinal fluid except when meninges are inflamed. Higher serum levels are obtained following I.M. injection. Most of the ampicillin is excreted unchanged in the urine and this excretion can be delayed by concurrent administration of probenecid. The active form appears in the bile in higher concentrations than found in the serum. TOTACILLIN (Ampicillin Trihydrate) is least serum bound of all the penicillins, averaging about 20% compared to approximately 60%-90% for other penicillins.

#### Indications

TOTACILLIN (Ampicillin Trihydrate) is indicated in the treatment of infections due to susceptible strains of the following:

*Gram-Negative Organisms*—*Shigellae*, *Salmonellae* (including *S. typhosa*), *H. influenzae*, *E. coli* and *P. mirabilis*, *N. gonorrhoeae*, and *N. meningitidis*.

*Gram-Positive Organisms*—Streptococci, *D. pneumoniae*, and non-penicillinase producing staphylococci.

Because of its wide spectrum and bactericidal action, it may be useful in instituting therapy; however, bacteriological studies to determine the causative organisms and their sensitivity to ampicillin should be performed. Indicated surgical procedures should be performed.

#### Contraindications

The use of this drug is contraindicated in individuals with a history of an allergic reaction to any of the penicillins.

#### Warnings

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL THERAPY, IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. THESE REACTIONS ARE MORE APT TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR HYPERSENSITIVITY REACTIONS TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE THERAPY WITH A PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, THE DRUG SHOULD BE DISCONTINUED AND THE PATIENT TREATED WITH THE USUAL AGENTS, e.g., PRESSOR AMINES, ANTIHISTAMINES, AND CORTICOSTEROIDS.

#### USAGE IN PREGNANCY:

Safety for use in pregnancy has not been established.

#### Precautions

As with any antibiotic preparation, constant observations for signs of overgrowth of nonsusceptible organisms, including fungi, are essential. Should superinfection occur (usually involving *Aerobacter*, *Pseudomonas*, or *Candida*), the drug should be discontinued and/or appropriate therapy instituted. As with any potent agent, it is advisable to check periodically for organ system dysfunction during prolonged therapy; this includes renal, hepatic, and hematopoietic systems. This is particularly important in prematures, neonates and other infants.

(continued on other side)



**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**Approval Package for:**

**APPLICATION NUMBER:**

**60-666 supplement**

Trade Name: Totacillin for Oral Suspension  
125mg/5mL and 250mg/5mL

Generic Name: ampicillin trihydrate

Sponsor: Beecham-Massengill

Approval Date: March 14, 1972

# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:**

**60-666 supplement**

## CONTENTS

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### Reviews / Information Included in this ANDA Review.

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Approval Letter(s)	X
Tentative Approval Letter(s)	
Final Printed Labeling	X
CSO Labeling Review(s)	
Medical Officer Review(s)	
Chemistry Review(s)	
Microbiology Review(s)	
Bioequivalence Review(s)	
Administrative Document(s)	
Correspondence	

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**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**APPROVAL LETTER**

①  
A-6 Doc  
~~XXXXXXXXXX~~

# Beecham-Massengill Pharmaceuticals

DIV. OF BEECHAM INC. CLIFTON, NEW JERSEY

65 INDUSTRIAL SOUTH  
CLIFTON, NEW JERSEY 07012

CABLE ADDRESS "BEECHPROD"  
TELEX 133471

PHONES NEW JERSEY 201-778-9000  
TENNESSEE 615-764-5141

*ok to pigmont  
JOP 3/14/72*

March 9, 1972

(For use of Food and Drug Administration)	
Date approved	<u>3/14/72</u>
Account No.	_____
Signed	<i>John P. Garrison</i>
For the Commissioner of Food and Drugs Food and Drug Administration (BD-145) Department of Health, Education, and Welfare	

Food and Drug Administration  
Bureau of Drugs  
Div. of Anti-Infective Drug Products  
Certifiable Drugs Review Unit  
5600 Fishers Lane  
Rockville, Maryland 20852

Re: #60-666 (146a.118) Supplement

Gentlemen:

Pursuant to Sections 140.14 and 130.9 of the Regulations, we hereby submit, in triplicate, a supplement to Beecham-Massengill Pharmaceuticals' approved Form 6 Application covering Totacillin (Ampicillin trihydrate) for Oral Suspension, 125mg./5cc. and 250mg./5cc.

This supplement provides for additional package sizes, 100cc. and 200cc. bottles; included are manufacturing directions, packaging standards, labels and the insert. The new package sizes will be instituted when the current 80cc. and 150cc. labeling inventories are phased out.

Sincerely yours,

BEECHAM-MASSENGILL PHARMACEUTICALS

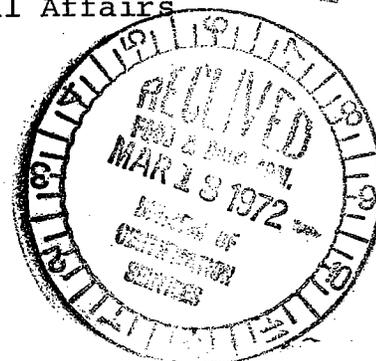
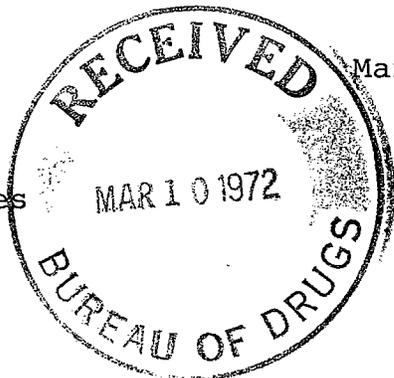
*George Vadnai*

George Vadnai  
Manager, Governmental Affairs

4802 ✓

GSV:dmm

Enclosures



**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**FINAL PRINTED LABELING**

## TOTACILLIN®

### AMPICILLIN TRIHYDRATE

for  
ORAL SUSPENSION

125 mg./5 cc.

and

250 mg./5 cc.

#### Description

TOTACILLIN (Ampicillin Trihydrate) is derived from the penicillin nucleus, 6-aminopenicillanic acid (6-APA), isolated by Beecham. Chemically it is D (-)  $\alpha$ -aminobenzyl penicillin.

#### Actions

#### MICROBIOLOGY:

TOTACILLIN (Ampicillin Trihydrate) is similar to benzyl penicillin in its bactericidal action against sensitive organisms during the stage of active multiplication. It acts through the inhibition of biosynthesis of cell wall mucopeptide. TOTACILLIN (Ampicillin Trihydrate) differs in *in vitro* spectrum from benzyl penicillin in the Gram-negative spectrum. It exerts high *in vitro* activity against many strains of *Hemophilus influenzae*, *Neisseria-gonorrhoeae*, *Neisseria meningitidis*, and *Neisseria catarrhalis*, *Escherichia coli*, *Proteus mirabilis*, *Bacteroides funduliformis*, *Salmonellae* and *Shigellae*.

*In vitro* studies have also demonstrated the sensitivity of many strains of the following Gram-positive bacteria: alpha- and beta-hemolytic streptococci, *Diplococcus pneumoniae*, non-penicillinase producing staphylococci, *Bacillus anthracis*, and most strains of enterococci and clostridia. Ampicillin generally provides less *in vitro* activity than penicillin-G against Gram-positive bacteria. Because it does not resist destruction by penicillinase, it is not effective against penicillinase producing bacteria, particularly resistant staphylococci. All strains of *Pseudomonas* and most strains of *Klebsiella* and *Aerobacter* are resistant.

#### PHARMACOLOGY:

TOTACILLIN (Ampicillin Trihydrate) is acid stable and therefore well absorbed. Food, however, retards absorption. Blood serum levels of approximately 2 mcg./ml. are attained within 1-2 hours following a 250 mg. oral dose given to fasting adults. Detectable amounts persist for about 6 hours. TOTACILLIN (Ampicillin Trihydrate) diffuses readily into all body tissues and fluids with the exception of brain and spinal fluid except when meninges are inflamed. Higher serum levels are obtained following I.M. injection. Most of the ampicillin is excreted unchanged in the urine and this excretion can be delayed by concurrent administration of probenecid. The active form appears in the bile in higher concentrations than found in the serum. TOTACILLIN (Ampicillin Trihydrate) is least serum bound of all the penicillins, averaging about 20% compared to approximately 60%-90% for other penicillins.

#### Indications

TOTACILLIN (Ampicillin Trihydrate) is indicated in the treatment of infections due to susceptible strains of the following:

*Gram-Negative Organisms*—*Shigellae*, *Salmonellae* (including *S. typhosa*), *H. influenzae*, *E. coli* and *P. mirabilis*, *N. gonorrhoeae*, and *N. meningitidis*.

*Gram-Positive Organisms*—Streptococci, *D. pneumoniae*, and non-penicillinase producing staphylococci.

Because of its wide spectrum and bactericidal action, it may be useful in instituting therapy; however, bacteriological studies to determine the causative organisms and their sensitivity to ampicillin should be performed.

Indicated surgical procedures should be performed.

#### Contraindications

The use of this drug is contraindicated in individuals with a history of an allergic reaction to any of the penicillins.

#### Warnings

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL THERAPY, IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. THESE REACTIONS ARE MORE APT TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR HYPERSENSITIVITY REACTIONS TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE THERAPY WITH A PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, THE DRUG SHOULD BE DISCONTINUED AND THE PATIENT TREATED WITH THE USUAL AGENTS, e.g., PRESSOR AMINES, ANTIHISTAMINES, AND CORTICOSTEROIDS.

#### USAGE IN PREGNANCY:

Safety for use in pregnancy has not been established.

#### Precautions

As with any antibiotic preparation, constant observations for signs of overgrowth of nonsusceptible organisms, including fungi, are essential. Should superinfection occur (usually involving *Aerobacter*, *Pseudomonas*, or *Candida*), the drug should be discontinued and/or appropriate therapy instituted. As with any potent agent, it is advisable to check periodically for organ system dysfunction during prolonged therapy; this includes renal, hepatic, and hematopoietic systems. This is particularly important in prematures, neonates, and other infants.

(continued on other side)

**TOTACILLIN®**  
**AMPICILLIN TRIHYDRATE**  
for  
**ORAL SUSPENSION**  
(continued from other side)

**Adverse Reactions**

As with other penicillins, it may be expected that untoward reactions will be essentially limited to sensitivity phenomena. They are more likely to occur in individuals who have previously demonstrated hypersensitivity to penicillins and in those with a history of allergy, asthma, hay fever, or urticaria. The following adverse reactions have been reported as associated with the use of ampicillin:

*Gastrointestinal*—Glossitis, Stomatitis, black "hairy" tongue, nausea, vomiting, and diarrhea. (These reactions are usually associated with oral dosage forms.)

*Hypersensitivity reactions*—An erythematous maculopapular rash has been reported fairly frequently. Urticaria and erythema multiforme have been reported occasionally. A few cases of exfoliative dermatitis have been reported. Anaphylaxis is the most serious reaction experienced and has usually been associated with the parenteral dosage form.

**Note:** Urticaria, other skin rashes, and serum sickness-like reactions may be controlled with antihistamines, and if necessary, systemic corticosteroids. Whenever such reactions occur, ampicillin should be discontinued, unless, in the opinion of the physician, the condition being treated is life-threatening and amenable only to ampicillin therapy. Serious anaphylactic reactions require the immediate use of epinephrine, oxygen, and intravenous steroids.

*Liver*—A moderate rise in serum glutamic oxaloacetic transaminase (SGOT) has been noted, particularly in infants, but the significance of this finding is unknown.

*Hemic and Lymphatic Systems*—Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia, and agranulocytosis have been reported during therapy with the penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be sensitivity reactions.

**Dosage**

*Infections of the ear, nose, throat, and lower respiratory tract* due to streptococci, pneumococci, and non-penicillinase producing staphylococci, and also those infections of the upper and lower respiratory tract due to *H. influenzae*:

Adults— 250 mg. every 6 hours.  
Children— 50 mg./kg./day in divided doses every 6 or 8 hours.

*Infections of the genitourinary tract caused by sensitive Gram-negative and Gram-positive bacteria:*

Adults— 500 mg. every 6 hours. Larger doses may be required for severe infections.  
Children— 100 mg./kg./day in divided doses every 6 hours.

*Urethritis due to N. gonorrhoeae:*

Adult Males—500 mg. every 8 hours.

*Cases of gonorrhea with a suspected lesion of syphilis should have dark-field examinations before receiving ampicillin, and monthly serological tests for a minimum of 4 months.*

*Infections of the gastrointestinal tract:*

Adults— 500 mg. every 6 hours.  
Children— 100 mg./kg./day in divided doses every 6 hours.

Larger doses may be required for stubborn or severe infections. The children's dosage is intended for individuals whose weight will not cause a dosage to be calculated greater than that recommended for adults. Children weighing more than 20 kg. should be dosed according to the adult recommendations. It should be recognized that in the treatment of chronic urinary tract and intestinal infections, frequent bacteriological and clinical appraisals are necessary. Smaller doses than those recommended above should not be used. Even higher doses may be needed at times. In stubborn infections, therapy may be required for several weeks. It may be necessary to continue clinical and/or bacteriological follow-up for several months after cessation of therapy.

Treatment should be continued for a minimum of 48 to 72 hours beyond the time that the patient becomes asymptomatic or evidence of bacterial eradication has been obtained. It is recommended that there be at least 10 days' treatment for any infection caused by hemolytic streptococci, to help prevent the occurrence of acute rheumatic fever or glomerulonephritis.

**Directions for Mixing Oral Suspension**

Prepare suspension at time of dispensing as follows: Add 66 cc. of water to the 100 cc. package and 132 cc. of water to the 200 cc. package. Shake vigorously. This will provide 100 and 200 cc. of suspension, respectively. Each teaspoonful (5 cc.) will contain 125 mg. or 250 mg. TOTACILLIN (Ampicillin Trihydrate). The reconstituted suspension is stable for 7 days at room temperature and 14 days under refrigeration.

**How Supplied**

TOTACILLIN (Ampicillin Trihydrate) for Oral Suspension. Each 5 cc. of reconstituted suspension contains ampicillin trihydrate equivalent to 125 mg. or 250 mg. ampicillin.

125 mg./5 cc.	250 mg./5 cc.
List No. 6625-23....100 cc. bottle	List No. 6630-23....100 cc. bottle
List No. 6625-24....200 cc. bottle	List No. 6630-24....200 cc. bottle

**Beecham-Massengill**  
PHARMACEUTICALS

DIV. OF BEECHAM INC. BRISTOL, TENN. 37620

**KEEP TIGHTLY CLOSED • SHAKE WELL BEFORE USING**  
When stored at room temperature discard unused portion after 7 days;  
when stored under refrigeration discard unused portion after 14 days.

Control No.

Exp. Date

Tear along perforation

**IMPORTANT:** Read accompanying literature for indications, dosage and precautions.

**CAUTION:** Federal law prohibits dispensing without prescription.

**KEEP TIGHTLY CLOSED • SHAKE WELL BEFORE USING**  
When stored at room temperature discard unused portion after 7 days;  
when stored under refrigeration discard unused portion after 14 days.

Control No.

Exp. Date

Tear along perforation

**IMPORTANT:** Read accompanying literature for indications, dosage and precautions.

**CAUTION:** Federal law prohibits dispensing without prescription.

NDC 29 6625 24  
**BMP**  
**TOTACILLIN<sup>®</sup>**  
Ampicillin Trihydrate  
for Oral Suspension

Equivalent to  
5.0 Gm. Ampicillin

When reconstituted  
each 5 cc. will contain

**125 mg.**

Ampicillin

200 cc. (6 $\frac{3}{4}$  fl. oz.)

*Beecham-Massengill*  
PHARMACEUTICALS  
DIV. OF BEECHAM INC. BRISTOL, TENN. 37620

TOTACILLIN<sup>®</sup> is a Registered Trademark

Directions for Mixing

Add 132 cc. of water and shake vigorously. Each 5 cc. (1 teaspoonful) contains ampicillin trihydrate equivalent to 125 mg. ampicillin.

Usual dosage—

Children: 50-100 mg./kg./day in divided doses every 6-8 hours.  
Adults: 250-500 mg. every 6 hours.

Made in U.S.A.

6447

NDC 29 6625 23  
**BMP**  
**TOTACILLIN<sup>®</sup>**  
Ampicillin Trihydrate  
for Oral Suspension

Equivalent to  
2.5 Gm. Ampicillin

When reconstituted  
each 5 cc. will contain

**125 mg.**

Ampicillin

100 cc. (3 $\frac{1}{2}$  fl. oz.)

*Beecham-Massengill*  
PHARMACEUTICALS  
DIV. OF BEECHAM INC. BRISTOL, TENN. 37620

TOTACILLIN<sup>®</sup> is a Registered Trademark

Directions for Mixing

Add 66 cc. of water and shake vigorously. Each 5 cc. (1 teaspoonful) contains ampicillin trihydrate equivalent to 125 mg. ampicillin.

Usual dosage—

Children: 50-100 mg./kg./day in divided doses every 6-8 hours.  
Adults: 250-500 mg. every 6 hours.

Made in U.S.A.

6448

**KEEP TIGHTLY CLOSED • SHAKE WELL BEFORE USING**

When stored at room temperature discard unused portion after 7 days;  
when stored under refrigeration discard unused portion after 14 days.

Control No.

Exp. Date

Tear along perforation

**IMPORTANT:** Read accompanying literature for indications, dosage and precautions.

**CAUTION:** Federal law prohibits dispensing without prescription.

**KEEP TIGHTLY CLOSED • SHAKE WELL BEFORE USING**

When stored at room temperature discard unused portion after 7 days;  
when stored under refrigeration discard unused portion after 14 days.

Control No.

Exp. Date

Tear along perforation

**IMPORTANT:** Read accompanying literature for indications, dosage and precautions.

**CAUTION:** Federal law prohibits dispensing without prescription.

NDC 29 6630 24  
**BMP**  
**TOTACILLIN®**  
Ampicillin Trihydrate  
for Oral Suspension

Equivalent to  
10.0 Gm. Ampicillin  
When reconstituted  
each 5 cc. will contain

**250 mg.**  
Ampicillin

200 cc. (6¾ fl. oz.)

*Beecham-Massengill*  
PHARMACEUTICALS  
DIV. OF BEECHAM INC BRISTOL, TENN. 37620

TOTACILLIN® is a Registered Trademark

Directions for Mixing

Add 132 cc. of water and shake vigorously. Each 5 cc. (1 teaspoonful) contains ampicillin trihydrate equivalent to 250 mg. ampicillin.

Usual dosage—

Children: 50-100 mg./kg./day in divided doses every 6-8 hours.  
Adults: 250-500 mg. every 6 hours.

Made in U.S.A.

6449

NDC 29 6630 23  
**BMP**  
**TOTACILLIN®**  
Ampicillin Trihydrate  
for Oral Suspension

Equivalent to  
5.0 Gm. Ampicillin  
When reconstituted  
each 5 cc. will contain

**250 mg.**  
Ampicillin

100 cc. (3⅓ fl. oz.)

*Beecham-Massengill*  
PHARMACEUTICALS  
DIV. OF BEECHAM INC BRISTOL, TENN. 37620

TOTACILLIN® is a Registered Trademark

Directions for Mixing

Add 66 cc. of water and shake vigorously. Each 5 cc. (1 teaspoonful) contains ampicillin trihydrate equivalent to 250 mg. ampicillin.

Usual dosage—

Children: 50-100 mg./kg./day in divided doses every 6-8 hours.  
Adults: 250-500 mg. every 6 hours.

Made in U.S.A.

6448

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**Approval Package for:**

**APPLICATION NUMBER:**

**60-666 supplement**

Trade Name: Alpen for Oral Suspension  
125mg/5mL and 250mg/5mL

Generic Name: ampicillin trihydrate

Sponsor: Beecham-Massengill

Approval Date: May 19, 1972

# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:**

**60-666 supplement**

## CONTENTS

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Reviews / Information Included in this ANDA Review.

---

Approval Letter(s)	X
Tentative Approval Letter(s)	
Final Printed Labeling	X
CSO Labeling Review(s)	
Medical Officer Review(s)	
Chemistry Review(s)	
Microbiology Review(s)	
Bioequivalence Review(s)	
Administrative Document(s)	
Correspondence	

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**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**APPROVAL LETTER**

①

A-6  
1. ~~Harvill~~  
2. ~~Ames~~

# Beecham-Massengill Pharmaceuticals

DIV. OF BEECHAM INC. CLIFTON, NEW JERSEY

65 INDUSTRIAL SOUTH  
CLIFTON, NEW JERSEY 07012

CABLE ADDRESS "BEECHPROD"  
TELEX 133471

PHONES NEW JERSEY 201-778-9000  
TENNESSEE 615-764-5141

*ok to sign out  
got 5/19/72*

May 17, 1972

Food and Drug Administration  
Bureau of Drugs  
Div. of Anti-Infective Drug Products  
Certifiable Drug Review Unit  
5600 Fishers Lane  
Rockville, Maryland 20852

(For use of Food and Drug Administration)

Date approved 5/19/72

Account No. \_\_\_\_\_

Signed John D. Hanson

For the Commissioner of Food and Drugs  
Food and Drug Administration  
Department of Health, Education, and Welfare

Re: 60-666 (146a.118) Supplement

Gentlemen:

Pursuant to Sections 140.14 and 130.9 of the Regulations we hereby submit, in triplicate, a supplement to Beecham-Massengill Pharmaceuticals' approved Form 6 Application covering Ampicillin trihydrate for Oral Suspension for 125mg./5cc. and 250mg./5cc.

Based on our previous supplement of March 9, 1972 (approved on March 14, 1972) for Totacillin for Oral Suspension, this supplement provides for the 100cc., 150cc., and 200cc. package sizes for the same product, distributed by Lederle Laboratories under the Alpen trade name.

The appropriate labeling is enclosed.

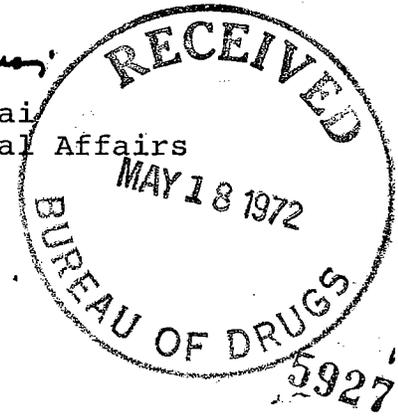


Sincerely yours,

BEECHAM-MASSENGILL PHARMACEUTICALS

*George Vadnai*

George Vadnai  
Manager, Governmental Affairs



GSV:dmm

Enclosures

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**FINAL PRINTED LABELING**

For Your Information and File  
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**KEEP TIGHTLY CLOSED  
 SHAKE WELL BEFORE USING**  
 When stored at room temperature discard unused portion after 7 days;  
 when stored under refrigeration discard unused portion after 14 days.  
 Control No. \_\_\_\_\_ Date Reconstituted \_\_\_\_\_



NDC 005-3840-46

**Alpen\***  
 Ampicillin Trihydrate  
 for

**Oral Suspension**

equivalent to  
 2.5 Grams Ampicillin  
**Cherry Flavored**  
 When Reconstituted  
 Each 5 cc will contain

**125 mg.**

Ampicillin  
 CAUTION: Federal law  
 prohibits dispensing  
 without prescription.

**100 cc** (when reconstituted)

Exp. Date \_\_\_\_\_

Directions for Mixing Prior to  
 Dispensing: Loosen powder, add a  
 total of 66 cc of water in two  
 portions and shake well after each  
 addition.  
 EACH 5 cc CONTAINS:  
 Ampicillin trihydrate equivalent to  
 125 mg Ampicillin.

USUAL DOSAGE:  
 Children:  
 50-100 mg./kg./day in divided doses  
 every 6-8 hours.

Adults:  
 250-500 mg every 6 hours.

IMPORTANT:  
 Read accompanying literature for  
 indications, dosage and precautions.

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 LEADER LABORATORIES  
 DIVISION  
 American Cyanamid Company  
 Pearl River, N.Y. 10965

RAR 167

DATE _____	FACSIMILE NO. _____
Composition No. _____	
Product/Pkg. No. _____	
Text Code No. _____	
Item _____	
Trimmed Size _____	
Tail Size _____	
Tint Size w/Bleed _____	
Tint Code No. _____	
Container No. _____	
Set Ups _____	
Paper Stock _____	
Grain Direction _____	
Color Instructions _____	
Varnish <input type="checkbox"/>	Perforate <input type="checkbox"/>
Back Up <input type="checkbox"/>	Die Cut <input type="checkbox"/>
Fold <input type="checkbox"/>	Score <input type="checkbox"/>
Folding Code _____	
Folding Instr. _____	
Final Fold Dimn. _____	
APPROVED _____	

*For Your Information and File*

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when stored under refrigeration discard unused portion after 14 days.  
Control No. \_\_\_\_\_ Date Reconstituted \_\_\_\_\_

Exp. Date \_\_\_\_\_



NDC 005-3840-60

**Alpen\***  
**Ampicillin Trihydrate**  
for  
**Oral Suspension**

equivalent to 5.0 Grams Ampicillin  
**Cherry Flavored**  
When Reconstituted Each 5 cc will contain

**125 mg. Ampicillin**

CAUTION: Federal law prohibits  
dispensing without prescription.

**200 cc (when reconstituted)**

Directions for Mixing Prior  
to Dispensing: Loosen  
powder; add a total of 132  
cc of water in two portions  
and shake well after each  
addition.

EACH 5 cc CONTAINS:  
Ampicillin trihydrate  
equivalent to 125 mg  
Ampicillin.

USUAL DOSAGE:

Children:

50-100 mg./kg./day in divided  
doses every 6-8 hours.

Adults:

250-500 mg every 6 hours.

IMPORTANT:

Read accompanying literature  
for indications, dosage  
and precautions.

Distributed by

**LEDERLE LABORATORIES  
DIVISION**

American Cyanamid Company  
Pearl River, N.Y. 10965

RAR 169

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DATE _____	FACSIMILE NO. _____
Composition No. _____	
Product/Pkg. No. _____	
Text Code No. _____	
Item _____	
Trimmed Size _____	
Tail Size _____	
Tint Size w/Bleed _____	
Tint Code No. _____	
Container No. _____	
Set Ups _____	
Paper Stock _____	
Grain Direction _____	
Color Instructions	
Varnish <input type="checkbox"/>	Perforate <input type="checkbox"/>
Back Up <input type="checkbox"/>	Die Cut <input type="checkbox"/>
Fold <input type="checkbox"/>	Score <input type="checkbox"/>
Folding Code _____	
Folding Instr. _____	
Final Fold Dimn. _____	
APPROVED _____	

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KEEP TIGHTLY CLOSED  
SHAKE WELL BEFORE USING  
When stored at room temperature discard unused portion after 7 days;  
when stored under refrigeration discard unused portion after 14 days.  
Control No. \_\_\_\_\_ Date Reconstituted \_\_\_\_\_



NDC 005-3841-46

**Alpen\***

**Ampicillin Trihydrate**

for

**Oral Suspension**

equivalent to  
5.0 Grams Ampicillin

**Cherry Flavored**

When Reconstituted  
Each 5 cc will contain

**250 mg.**

Ampicillin

CAUTION: Federal law  
prohibits dispensing  
without prescription.

**100 cc** (when reconstituted)

Exp. Date \_\_\_\_\_

RAR 164

Directions for Mixing Prior to  
Dispensing: Loosen powder, add a  
total of 56 cc of water in two  
portions and shake well after each  
addition.

EACH 5 cc CONTAINS:  
Ampicillin trihydrate equivalent to  
250 mg Ampicillin.

USUAL DOSAGE:

Children:  
50-100 mg./kg./day in divided doses  
every 6-8 hours.

Adults:  
250-500 mg every 6 hours.

IMPORTANT:

Read accompanying literature for  
indications, dosage and precautions.

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DIVISION  
American Cyanamid Company  
Pearl River, N.Y. 10965

Composition No. \_\_\_\_\_

Product/Pkg. No. \_\_\_\_\_

Text Code No. \_\_\_\_\_

Item \_\_\_\_\_

Trimmed Size \_\_\_\_\_

Tail Size \_\_\_\_\_

Tint Size w/Bleed \_\_\_\_\_

Tint Code No. \_\_\_\_\_

Container No. \_\_\_\_\_

Set Ups \_\_\_\_\_

Paper Stock \_\_\_\_\_

Grain Direction \_\_\_\_\_

Color Instructions

Varnish	<input type="checkbox"/>	Perforate	<input type="checkbox"/>
Back Up	<input type="checkbox"/>	Die Cut	<input type="checkbox"/>
Fold	<input type="checkbox"/>	Score	<input type="checkbox"/>

Folding Code \_\_\_\_\_

Folding Instr. \_\_\_\_\_

Final Fold Dimn. \_\_\_\_\_

APPROVED

For Your Information and File

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**KEEP TIGHTLY CLOSED  
SHAKE WELL BEFORE USING**  
When stored at room temperature discard unused portion after 7 days;  
when stored under refrigeration discard unused portion after 14 days.  
Date Reconstituted  
Control No.

Exp. Date



NDC 005-3841-49

**Alpen\***  
**Ampicillin  
Trihydrate**  
for  
**Oral Suspension**

equivalent to  
7.5 Grams Ampicillin  
**Cherry Flavored**  
When Reconstituted  
Each 5 cc will contain

**250 mg.**

Ampicillin  
CAUTION: Federal law  
prohibits dispensing  
without prescription.

**150 cc** (when reconstituted)

Directions for Mixing Prior to  
Dispensing: Loosen powder, add  
a total of 100 cc of water in two  
portions and shake well after each  
addition.

EACH 5 cc CONTAINS:  
Ampicillin trihydrate equivalent  
to 250 mg Ampicillin.

**USUAL DOSAGE:**

Children:  
50-100 mg./kg./day in divided  
doses every 6-8 hours.

Adults:  
250-500 mg every 6 hours.

**IMPORTANT:**  
Read accompanying literature  
for indications, dosage  
and precautions.

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American Cyanamid Company  
Pearl River, N.Y. 10965

RAR165

DATE	FACSIMILE NO.
Composition No. _____	
Product/Pkg. No. _____	
Text Code No. _____	
Item _____	
Trimmed Size _____	
Tail Size _____	
Tint Size w/Bleed _____	
Tint Code No. _____	
Container No. _____	
Set Ups _____	
Paper Stock _____	
Grain Direction _____	
Color Instructions	
Varnish <input type="checkbox"/>	Perforate <input type="checkbox"/>
Back Up <input type="checkbox"/>	Die Cut <input type="checkbox"/>
Fold <input type="checkbox"/>	Score <input type="checkbox"/>
Folding Code _____	
Folding Instr. _____	
Final Fold Dimn. _____	
APPROVED	

For Your Information and File

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KEEP TIGHTLY CLOSED  
SHAKE WELL BEFORE USING

When stored at room temperature, discard unused portion after 7 days;  
When stored under refrigeration, discard unused portion after 14 days.  
Control No. \_\_\_\_\_  
Date Reconstituted \_\_\_\_\_

Exp. Date \_\_\_\_\_



NDC 005-3841-60

# Alpen\*

## Ampicillin Trihydrate

for

### Oral Suspension

equivalent to 10.0 Grams Ampicillin

**Cherry Flavored**

When Reconstituted Each 5 cc will contain

**250 mg.** Ampicillin

CAUTION: Federal law prohibits dispensing without prescription.

**200 cc** (when reconstituted)

Directions for Mixing Prior to Dispensing: Loosen powder, add a total of 132 cc of water in two portions and shake well after each addition.

EACH 5 cc CONTAINS: Ampicillin trihydrate equivalent to 250 mg Ampicillin.

USUAL DOSAGE:

Children:

50-100 mg./kg./day in divided doses every 6-8 hours.

Adults:

250-500 mg every 6 hours.

IMPORTANT:

Read accompanying literature for indications, dosage and precautions.

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PAR166

DATE _____	FACSIMILE NO. _____
Composition No. _____	
Product/Pkg. No. _____	
Text Code No. _____	
Item _____	
Trimmed Size _____	
Tail Size _____	
Tint Size w/Bleed _____	
Tint Code No. _____	
Container No. _____	
Set Ups _____	
Paper Stock _____	
Grain Direction _____	
Color Instructions _____	
Varnish <input type="checkbox"/>	
Perforate <input type="checkbox"/>	
Back Up <input type="checkbox"/>	
Die Cut <input type="checkbox"/>	
Fold <input type="checkbox"/>	
Score <input type="checkbox"/>	
Folding Code _____	
Folding Instr. _____	
Final Fold Dimn. _____	
APPROVED _____	

**ALPEN\***  
**AMPICILLIN TRIHYDRATE**  
**FOR**  
**ORAL SUSPENSION**  
**125 mg./5 cc.**  
**and**  
**250 mg./5 cc.**

**DESCRIPTION**

ALPEN *ampicillin trihydrate* is derived from the penicillin nucleus, 6-amino-penicillanic acid (6-APA). Chemically it is D (-)  $\alpha$ -amino-benzylpenicillin.

**ACTIONS****MICROBIOLOGY:**

Ampicillin Trihydrate is similar to benzyl penicillin in its bactericidal action against sensitive organisms during the stage of active multiplication. It acts through the inhibition of biosynthesis of cell wall mucopeptide. Ampicillin Trihydrate differs in *in vitro* spectrum from benzylpenicillin in the Gram negative spectrum. It exerts high *in vitro* activity against many strains of *Hemophilus influenzae*, *Neisseria gonorrhoeae*, *Neisseria meningitidis* and *Neisseria catarrhalis*, *Escherichia coli*, *Proteus mirabilis*, *Bacteroides funduliformis*, *Salmonellae*, and *Shigellae*.

*In vitro* studies have also demonstrated the sensitivity of many strains of the following Gram positive bacteria: alpha- and beta-hemolytic streptococci, *Diplococcus pneumoniae*, non-penicillinase producing staphylococci, *Bacillus anthracis*, and most strains of enterococci and clostridia. Ampicillin generally provides less *in vitro* activity than penicillin-G against Gram positive bacteria. Because it does not resist destruction by penicillinase it is *not* effective against penicillinase producing bacteria, particularly resistant staphylococci. All strains of *Pseudomonas* and most strains of *Klebsiella* and *Aerobacter* are resistant.

**PHARMACOLOGY:**

ALPEN *ampicillin trihydrate* is acid stable and therefore well absorbed. Food, however, retards absorption. Blood serum levels of approximately 2 mcg./ml. are attained within 1-2 hours following a 250 mg. oral dose given to fasting adults. Detectable amounts persist for about 6 hours. Ampicillin Trihydrate diffuses readily into all body tissues and fluids with the exception of brain and spinal fluid except when meninges are inflamed. Higher serum levels are obtained following I.M. injection. Most of the ampicillin is excreted unchanged in the urine and this excretion can be delayed by concurrent administration of probenecid. The active form appears in the bile in higher concentrations than found in the serum. Ampicillin Trihydrate is least serum bound of all the penicillin, averaging about 20% compared to approximately 60%-90% for other penicillins.

**INDICATIONS**

ALPEN *ampicillin trihydrate* is indicated in the treatment of infections due to susceptible strains of the following:

*Gram Negative Organisms - Shigellae, Salmonellae (including S. typhosa), H. influenzae, E. coli, P. mirabilis, N. gonorrhoeae and N. meningitidis.*

*Gram Positive Organisms - Streptococci, D. pneumoniae, and non-penicillinase producing staphylococci.*

Because of its wide spectrum and bactericidal action, it may be useful in instituting therapy; however, bacteriological studies to determine the causative organisms and their sensitivity to ampicillin should be performed.

Indicated surgical procedures should be performed.

**CONTRAINDICATIONS**

The use of this drug is contraindicated in individuals with a history of an allergic reaction to any of the penicillins.

**WARNINGS**

**SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL THERAPY IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. THESE REACTIONS ARE MORE APT TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR HYPERSENSITIVITY REACTIONS TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE THERAPY WITH A PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, THE DRUG SHOULD BE DISCONTINUED AND THE PATIENT TREATED WITH THE USUAL AGENTS, e.g., PRESSOR AMINES, ANTIHISTAMINES, AND CORTICOSTEROIDS.**

**USAGE IN PREGNANCY:**

Safety for use in pregnancy has not been established.

**PRECAUTIONS**

As with any antibiotic preparation, constant observations for signs of overgrowth of nonsusceptible organism, including fungi, is essential. Should superinfection occur (usually involving *Aerobacter*, *Pseudomonas*, or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.

As with any potent agent, it is advisable to check periodically for organ system dysfunction during prolonged therapy; this includes renal, hepatic, and hematopoietic systems. This is particularly important in pre-matures, neonates and other infants.

**ADVERSE REACTIONS**

As with other penicillins, it may be expected that untoward reactions will be essentially limited to sensitivity phenomena. They are more likely to occur in individuals who have previously demonstrated hypersensitivity to penicillins and in those with a history of allergy, asthma, hay fever, or urticaria.

The following adverse reactions have been reported as associated with the use of ampicillin:

*Gastrointestinal, Glossitis, Stomatitis, Black "hairy" tongue, nausea, vomiting, diarrhea.* (These reactions are usually associated with oral dosage forms).

*Hypersensitivity Reactions* - An erythematous maculopapular rash has been reported fairly frequently. Urticaria and erythema multiforme have been reported occasionally. A few cases of exfoliative dermatitis have been reported. Anaphylaxis is the most serious reaction experienced and has usually been associated with the parenteral dosage form.

#### NOTE:

Urticaria, other skin rashes, and serum sickness-like reactions may be controlled with antihistamines, and if necessary, systemic corticosteroids. Whenever such reactions occur, ampicillin should be discontinued, unless, in the opinion of the physician, the condition being treated is life threatening and amenable only to ampicillin therapy. Serious anaphylactic reactions require the immediate use of epinephrine, oxygen, and intravenous steroids.

*LIVER* - A moderate rise in serum glutamic oxaloacetic transaminase (SGOT) has been noted, particularly in infants, but the significance of this finding is unknown.

*HEMIC AND LYMPHATIC SYSTEMS*—Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leucopenia, and agranulocytosis have been reported during therapy with the penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be sensitivity reactions.

#### DOSAGE

*Infections of the ear, nose, throat, and lower respiratory tract due to streptococci, pneumococci, and non-penicillinase producing staphylococci; and also those infections of the upper and lower respiratory tract due to H. influenzae.*

Adults: 250 mg. every 6 hours.

Children: 50 mg./kg./day in divided doses every 6 or 8 hours.

*Infections of the genitourinary tract caused by sensitive Gram negative and Gram positive bacteria.*

Adults: 500 mg. every 6 hours. Larger doses may be required for severe infections.

Children: 100 mg./kg./day in divided doses every 6 hours.

*Urethritis due to N. gonorrhoeae.*

Adult Males: 500 mg. every 8 hours.

*Cases of gonorrhea with a suspected lesion of syphilis should have dark-field examinations before receiving ampicillin, and monthly serological tests for a minimum of 4 months.*

*Infections of the gastrointestinal tract.*

Adults: 500 mg. every 6 hours.

Children: 100 mg./kg./day in divided doses every 6 hours.

Larger doses may be required for stubborn or severe infections. The children's dosage is intended for individuals whose weight will not cause a dosage to be calculated greater than that recommended for adults. Children weighing more than 20 kg. should be dosed according to the adult recommendations.

It should be recognized that in the treatment of chronic urinary tract and intestinal infections, frequent bacteriological and clinical appraisal are necessary. Smaller doses than those recommended above should not be used. Even higher doses may be needed at times. In stubborn infections, therapy may be required for several weeks. It may be necessary to continue clinical and/or bacteriological follow-up for several months after cessation of therapy.

Treatment should be continued for a minimum of 48 to 72 hours beyond the time that the patient becomes asymptomatic or evidence of bacterial eradication has been obtained. It is recommended that there be at least 10 days' treatment for any infection caused by hemolytic streptococci, to help prevent the occurrence of acute rheumatic fever or glomerulonephritis.

#### DIRECTIONS for MIXING ORAL SUSPENSION

Prepare either strength suspension at time of dispensing as follows: Add 53 cc. of water to the 80 cc. package; 66 cc. of water to the 100 cc. package; 100 cc. of water to the 150 cc. package; 132 cc. of water to the 200 cc. package. Shake vigorously. This will provide 80 cc.; 100 cc.; 150 cc. or 200 cc. of suspension respectively. Each teaspoonful (5 cc.) will contain 125 mg. or 250 mg. ampicillin. The reconstituted suspension is stable for 7 days at room temperature and 14 days under refrigeration.

#### HOW SUPPLIED

ALPEN ampicillin trihydrate for Oral Suspension. Each 5 cc. of reconstituted suspension contains ampicillin trihydrate equivalent to 125 mg. or 250 mg. ampicillin.

125 mg./5 cc. - Product No. 3840, bottles of 80 cc., 100 cc., 150 cc. and 200 cc.

250 mg./5 cc. - Product No. 3841, bottles of 80 cc., 100 cc., 150 cc. and 200 cc.



Distributed by

**LEDERLE LABORATORIES DIVISION**

**American Cyanamid Company, Pearl River, N.Y. 10965**

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**Approval Package for:**

**APPLICATION NUMBER:**

**60-666 supplement**

Trade Name: Totacillin for Oral Suspension  
125mg/5mL and 250mg/5mL

Generic Name: ampicillin trihydrate

Sponsor: Beecham-Massengill

Approval Date: May 30, 1972

# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:**

**60-666 supplement**

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**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**APPROVAL LETTER**

# Beecham-Massengill Pharmaceuticals

DIV. OF BEECHAM INC. CLIFTON, NEW JERSEY

65 INDUSTRIAL SOUTH  
CLIFTON, NEW JERSEY 07012

CABLE ADDRESS "BEECHPROD"  
TELEX 133471

PHONES NEW JERSEY 201-778-9000  
TENNESSEE 615-764-5141

February 29, 1972

Date Approved 5/30/72

Account No. \_\_\_\_\_

Mr. Milton Eisler  
Food and Drug Administration  
Division of Certification Services (BD-145)  
5600 Fishers Lane  
Rockville, Maryland 20852

Signed George Vadnai  
For the Commissioner of Food and Drug  
Department of Health, Education and  
Welfare

Re: #60-666 (146a.118)

Dear Mr. Eisler:

Reference is made to Beecham-Massengill Pharmaceuticals' approved Form 6 Application, covering Totacillin® (Ampicillin trihydrate) for Oral Suspension, 125mg./5cc. and 250mg./5cc.

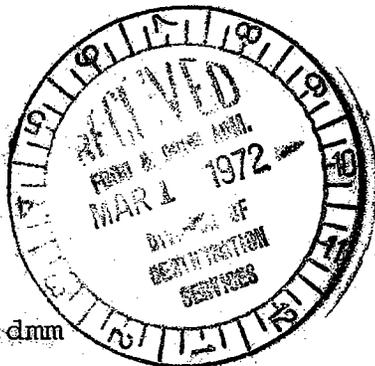
In accordance with our agreement of July 15, 1971, we are hereby submitting, in triplicate, the results (and all other appropriate data) of a three-way study, comparing the stability of a proposed new formulation with our current product and the originally submitted \_\_\_\_\_ containing formula. The data clearly indicates that the stability of the new formula is superior to those of the other two. In addition, we are submitting 30 months stability data for the \_\_\_\_\_ formula. Since the stability of the new, proposed formula is superior to the one containing \_\_\_\_\_, and the difference from the current composition is so minor, that new bioequivalency data is not required, we request approval for this formula with a 24 months expiration date.

Sincerely yours,

BEECHAM-MASSENGILL PHARMACEUTICALS

George Vadnai

George Vadnai  
Manager, Governmental Affairs



GSV:dmm

Enclosures

4600

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**Approval Package for:**

**APPLICATION NUMBER:**

**60-666 supplement**

Trade Name: Pen A for Oral Suspension  
125mg/5mL and 150mg/5mL

Generic Name: ampicillin trihydrate

Sponsor: Beecham-Massengill

Approval Date: June 8, 1972

# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:**

**60-666 supplement**

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**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**APPROVAL LETTER**

(1)

# Beecham-Massengill Pharmaceuticals

DIV. OF BEECHAM INC. CLIFTON, NEW JERSEY

65 INDUSTRIAL SOUTH  
CLIFTON, NEW JERSEY 07012

CABLE ADDRESS "BEECHPROD"  
TELEX 133471

NEW JERSEY 201-778-9000  
TENNESSEE 615-764-5141

*OK to sign out  
JOP 6/8/72*

June 5, 1972

Food and Drug Administration  
Certifiable Drug Review Staff (BD-115)  
Div. of Anti-Infective Drug Products  
5600 Fishers Lane  
Rockville, Maryland 20852

(For use of Food and Drug Administration)	
Date approved	6/8/72
Account No.	
Signed	<i>John D. Garrison</i>
For the Commissioner of Food and Drugs Food and Drug Administration Department of Health, Education, and Welfare	
Re:	<del>60-660 (146a.7)</del> <u>60-666 (146a.118)</u> <u>60-677 (146a.119)</u>

Gentlemen:

Reference is made to Beecham-Massengill Pharmaceuticals' approved Form 6 Applications covering Totacillin (Ampicillin trihydrate) Capsules and for Oral Suspension, and Totacillin-N (Sodium Ampicillin) for Injection.

We hereby submit, in triplicate, the final printed labeling for Pen A Capsules, for Oral Suspension, and Pen A/N for Injection. (re: our supplement of May 2, 1972 and your letter of May 8, 1972).

Sincerely yours,

BEECHAM-MASSENGILL PHARMACEUTICALS

*G. Vadnai*

George Vadnai  
Manager, Governmental Affairs

GSV:dmm

Enclosures

✓

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**FINAL PRINTED LABELING**

9026

Professional Sample

3 Bottles

**Pen A™**  
ampicillin trihydrate  
FOR ORAL SUSPENSION  
250 mg.†

CAUTION: Federal law prohibits dispensing without prescription.  
Distributed by

**Pfizer**

**LABORATORIES DIVISION**  
PFIZER INC., NEW YORK, N.Y. 10017

55-2094-00-0

MADE IN U.S.A.

**PFIZER**

12345  
67890



Directions for reconstitution: Add 7½ teaspoonful (3.3cc) water to vial and shake vigorously. † The resultant suspension contains ampicillin trihydrate equivalent to 250 mg. ampicillin.

**USUAL DOSAGE**  
Children: 50 to 100 mg./kg./day in divided doses every 6 to 8 hours.  
Adults: 250 to 500 mg. every 6 hours.

READ ACCOMPANYING PROFESSIONAL INFORMATION

Professional Sample

**Pen A**<sup>TM</sup>  
ampicillin trihydrate  
FOR ORAL SUSPENSION  
250 mg. †



3 Bottles

Exp.  
Lot No.  
KEEP TIGHTLY CLOSED  
SHAKE WELL BEFORE USING

Professional Sample  
**Pen A™**  
ampicillin trihydrate  
FOR ORAL SUSPENSION  
250 mg.†  
CAUTION: Federal law prohibits  
dispensing without prescription.  
Distributed by  
  
LABORATORIES DIVISION  
PFIZER INC., NEW YORK, N.Y. 10017

Directions for reconstitution: Add 5 teaspoonful (20 cc.) water and shake well. The resulting suspension contains ampicillin trihydrate equivalent to 250 mg. ampicillin.  
USUAL DOSAGE  
Children: 50 to 100 mg./kg./day in divided doses every 6 to 8 hours.  
Adults: 250 to 500 mg. every 6 hours.  
READ ACCOMPANYING PROFESSIONAL INFORMATION  
MADE IN U.S.A.

Exp.  
Lot No.  
KEEP TIGHTLY CLOSED—SHAKE WELL BEFORE USING  
When suspension is stored at room temperature discard unused portion after 7 days; when stored under refrigeration discard unused portion after 14 days.

NDC 069-0312-44 100 cc.  
2396  
**Pen A™**  
ampicillin trihydrate  
FOR ORAL SUSPENSION  
Equivalent to  
5.0 Gm. ampicillin  
**250 mg./5 cc.†**  
CAUTION: Federal law prohibits  
dispensing without prescription.  
Distributed by  
  
LABORATORIES DIVISION  
PFIZER INC.  
NEW YORK, N.Y. 10017

READ ACCOMPANYING PROFESSIONAL INFORMATION

†When reconstituted as directed each 5 cc. (1 teaspoonful) contains ampicillin trihydrate equivalent to 250 mg. ampicillin.  
Directions for reconstitution: Add 66 cc. of water. For ease of preparation, tap gently, add water in 2 portions. Shake well after each addition.  
USUAL DOSAGE: Children: 50 to 100 mg./kg./day in divided doses every 6 to 8 hours.  
Adults: 250 to 500 mg. every 6 hours.  
MADE IN U.S.A. 0 9019

Exp.  
Lot No.  
KEEP TIGHTLY CLOSED—SHAKE WELL BEFORE USING  
When suspension is stored at room temperature discard unused portion after 7 days; when stored under refrigeration discard unused portion after 14 days.

NDC 069-0312-91 200 cc.  
2397  
**Pen A™**  
ampicillin trihydrate  
FOR ORAL SUSPENSION  
Equivalent to  
10.0 Gm. ampicillin  
**250 mg./5 cc.†**  
CAUTION: Federal law prohibits  
dispensing without prescription.  
Distributed by  
  
LABORATORIES DIVISION  
PFIZER INC.  
NEW YORK, N.Y. 10017

READ ACCOMPANYING PROFESSIONAL INFORMATION

†When reconstituted as directed each 5 cc. (1 teaspoonful) contains ampicillin trihydrate equivalent to 250 mg. ampicillin.  
Directions for reconstitution: Add 132 cc. of water. For ease of preparation, tap gently, add water in 2 portions. Shake well after each addition.  
USUAL DOSAGE  
Children: 50 to 100 mg./kg./day in divided doses every 6 to 8 hours.  
Adults: 250 to 500 mg. every 6 hours.  
MADE IN U.S.A. 0 9013

Exp.  
Lot No.

**KEEP TIGHTLY CLOSED—SHAKE WELL BEFORE USING**  
When suspension is stored at room temperature discard unused portion after 7 days; when stored under refrigeration discard unused portion after 14 days.

READ ACCOMPANYING PROFESSIONAL INFORMATION

NDC 069-0311-44 100 cc.  
2394

# Pen A<sup>TM</sup> ampicillin trihydrate

**FOR ORAL SUSPENSION**

Equivalent to  
2.5 Gm. ampicillin

**125 mg./5 cc.<sup>†</sup>**

CAUTION: Federal law prohibits dispensing without prescription.  
Distributed by



<sup>†</sup>When reconstituted as directed each 5 cc. (1 teaspoonful) contains ampicillin trihydrate equivalent to 125 mg. ampicillin.

Directions for reconstitution: Add 66 cc. of water. For ease of preparation, tap gently, add water in 2 portions. Shake well after each addition.

**USUAL DOSAGE:** Children: 50 to 100 mg./kg./day in divided doses every 6 to 8 hours.  
Adults: 250 to 500 mg. every 6 hours.

MADE IN U.S.A. 9022

Exp.

Lot No.

**KEEP TIGHTLY CLOSED—SHAKE WELL BEFORE USING**  
When suspension is stored at room temperature discard unused portion after 7 days; when stored under refrigeration discard unused portion after 14 days.

READ ACCOMPANYING PROFESSIONAL INFORMATION

NDC 069-0311-91 200 cc.  
2395

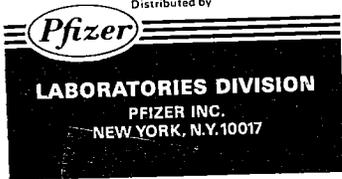
# Pen A<sup>TM</sup> ampicillin trihydrate

**FOR ORAL SUSPENSION**

Equivalent to  
5.0 Gm. ampicillin

**125 mg./5 cc.<sup>†</sup>**

CAUTION: Federal law prohibits dispensing without prescription.  
Distributed by



<sup>†</sup>When reconstituted as directed each 5 cc. (1 teaspoonful) contains ampicillin trihydrate equivalent to 125 mg. ampicillin.

Directions for reconstitution: Add 132 cc. of water. For ease of preparation, tap gently, add water in 2 portions. Shake well after each addition.

**USUAL DOSAGE**  
Children: 50 to 100 mg./kg./day in divided doses every 6 to 8 hours.  
Adults: 250 to 500 mg. every 6 hours.

MADE IN U.S.A. 9016

Exp.

Lot No.

**KEEP TIGHTLY CLOSED—SHAKE WELL BEFORE USING**  
When suspension is stored at room temperature discard unused portion after 7 days; when stored under refrigeration discard unused portion after 14 days.

READ ACCOMPANYING PROFESSIONAL INFORMATION

NDC 069-0312-91 200 cc.  
2397

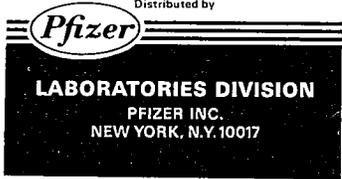
# Pen A<sup>TM</sup> ampicillin trihydrate

**FOR ORAL SUSPENSION**

Equivalent to  
10.0 Gm. ampicillin

**250 mg./5 cc.<sup>†</sup>**

CAUTION: Federal law prohibits dispensing without prescription.  
Distributed by



<sup>†</sup>When reconstituted as directed each 5 cc. (1 teaspoonful) contains ampicillin trihydrate equivalent to 250 mg. ampicillin.

Directions for reconstitution: Add 132 cc. of water. For ease of preparation, tap gently, add water in 2 portions. Shake well after each addition.

**USUAL DOSAGE**  
Children: 50 to 100 mg./kg./day in divided doses every 6 to 8 hours.  
Adults: 250 to 500 mg. every 6 hours.

MADE IN U.S.A. 9013

Pfizer

Pen A™

Pfizer

## ampicillin trihydrate

CAPSULES

250 mg.

and

500 mg.

for

ORAL SUSPENSION

125 mg./5 cc.

and

250 mg./5 cc.

**Description**

Pen A (ampicillin trihydrate) is derived from the penicillin nucleus, 6-aminopenicillanic acid (6-APA). Chemically it is D (-)  $\alpha$ -aminobenzyl penicillin.

**Actions****MICROBIOLOGY:**

Pen A (ampicillin trihydrate) is similar to benzyl penicillin in its bactericidal action against sensitive organisms during the stage of active multiplication. It acts through the inhibition of biosynthesis of cell wall mucopeptide. Pen A (ampicillin trihydrate) differs in *in vitro* spectrum from benzyl penicillin in the gram-negative spectrum. It exerts high *in vitro* activity against many strains of *Hemophilus influenzae*, *Neisseria gonorrhoeae*, *Neisseria meningitidis* and *Neisseria catarrhalis*, *Escherichia coli*, *Proteus mirabilis*, *Bacteroides funduliformis*, *Salmonellae* and *Shigellae*.

*In vitro* studies have also demonstrated the sensitivity of many strains of the following gram-positive bacteria: alpha- and beta-hemolytic streptococci, *Diplococcus pneumoniae*, nonpenicillinase-producing staphylococci, *Bacillus anthracis*, and most strains of enterococci and clostridia. Ampicillin generally provides less *in vitro* activity than penicillin G against gram-positive bacteria. Because it does not resist destruction by penicillinase, it is not effective against penicillinase-producing bacteria, particularly resistant staphylococci. All strains of *Pseudomonas* and most strains of *Klebsiella* and *Aerobacter* are resistant.

**PHARMACOLOGY:**

Pen A (ampicillin trihydrate) is acid stable and therefore well absorbed. Food, however, retards absorption. Blood serum levels of approximately 2 mcg./ml. are attained within 1-2 hours following a 250 mg. oral dose given to fasting adults. Detectable amounts persist for about 6 hours. Pen A (ampicillin trihydrate) diffuses readily into all body tissues and fluids with the exception of brain and spinal fluid except when meninges are inflamed. Higher serum levels are obtained following IM. injection. Most of the ampicillin is excreted unchanged in the urine and this excretion can be delayed by concurrent administration of probenecid. The active form appears in the bile in higher concentrations than found in the serum. Pen A (ampicillin trihydrate) is the least serum bound of all the penicillins, averaging about 20% compared to approximately 60%-90% for other penicillins.

**Indications**

Pen A (ampicillin trihydrate) is indicated in the treatment of infections due to susceptible strains of the following:

*gram-negative organisms*—*Shigellae*, *Salmonellae* (including *S. typhosa*), *H. influenzae*, *E. coli* and *P. mirabilis*, *N. gonorrhoeae*, and *N. meningitidis*;

*gram-positive organisms*—Streptococci, *D. pneumoniae*, and nonpenicillinase-producing staphylococci.

Because of its wide spectrum and bactericidal action, it may be useful in instituting therapy; however, bacteriological studies to determine the causative organisms and their sensitivity to ampicillin should be performed.

Indicated surgical procedures should be performed.

**Contraindications**

The use of this drug is contraindicated in individuals with a history of an allergic reaction to any of the penicillins.

**Warnings**

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL THERAPY, IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. THESE REACTIONS ARE MORE APT TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR HYPERSENSITIVITY REACTIONS TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE THERAPY WITH A PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, THE DRUG SHOULD BE DISCONTINUED AND THE PATIENT TREATED WITH THE USUAL AGENTS, e.g., PRESSOR AMINES, ANTIHISTAMINES, AND CORTICOSTEROIDS.

**USAGE IN PREGNANCY:**

Safety for use in pregnancy has not been established.

**Precautions**

As with any antibiotic preparation, constant observations for signs of overgrowth of nonsusceptible organisms, including fungi, are essential. Should superinfection occur (usually involving *Aerobacter*, *Pseudomonas*, or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.

### **Precautions (continued)**

As with any potent agent, it is advisable to check periodically for organ system dysfunction during prolonged therapy; this includes renal, hepatic, and hematopoietic systems. This is particularly important in prematures, neonates and other infants.

### **Adverse Reactions**

As with other penicillins, it may be expected that untoward reactions will be essentially limited to sensitivity phenomena. They are more likely to occur in individuals who have previously demonstrated hypersensitivity to penicillins and in those with a history of allergy, asthma, hay fever, or urticaria. The following adverse reactions have been reported as associated with the use of ampicillin:

**Gastrointestinal**—glossitis, stomatitis, black "hairy" tongue, nausea, vomiting, and diarrhea. (These reactions are usually associated with oral dosage forms.)

**Hypersensitivity reactions**—An erythematous maculopapular rash has been reported fairly frequently. Urticaria and erythema multiforme have been reported occasionally. A few cases of exfoliative dermatitis have been reported. Anaphylaxis is the most serious reaction experienced and has usually been associated with the parenteral dosage form.

**Note:** Urticaria, other skin rashes, and serum sickness-like reactions may be controlled with antihistamines, and if necessary, systemic corticosteroids. Whenever such reactions occur, ampicillin should be discontinued, unless, in the opinion of the physician, the condition being treated is life-threatening and amenable only to ampicillin therapy. Serious anaphylactic reactions require the immediate use of epinephrine, oxygen, and intravenous steroids.

**Liver**—A moderate rise in serum glutamic oxaloacetic transaminase (SGOT) has been noted, particularly in infants, but the significance of this finding is unknown.

**Hemic and Lymphatic Systems**—Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia, and agranulocytosis have been reported during therapy with the penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be sensitivity reactions.

### **Dosage**

**Infections of the ear, nose, throat, and lower respiratory tract** due to streptococci, pneumococci, and nonpenicillinase-producing staphylococci, and also those infections of the upper and lower respiratory tract due to *H. influenzae*:

Adults— 250 mg. every 6 hours.

Children— 50 mg./kg./day in divided doses every 6 or 8 hours.

**Infections of the genitourinary tract caused by sensitive gram-negative and gram-positive bacteria:**

Adults— 500 mg. every 6 hours. Larger doses may be required for severe infections.

Children— 100 mg./kg./day in divided doses every 6 hours.

**Urethritis due to *N. gonorrhoeae*:**

Adult Males— 500 mg. every 8 hours.

**Cases of gonorrhea with a suspected lesion of syphilis should have dark field examinations before receiving ampicillin, and monthly serological tests for a minimum of 4 months.**

**Infections of the gastrointestinal tract:**

Adults— 500 mg. every 6 hours.

Children— 100 mg./kg./day in divided doses every 6 hours.

Larger doses may be required for stubborn or severe infections. The children's dosage is intended for individuals whose weight will not cause a dosage to be calculated greater than that recommended for adults. Children weighing more than 20 kg. should be dosed according to the adult recommendations.

It should be recognized that in the treatment of chronic urinary tract and intestinal infections, frequent bacteriological and clinical appraisal are necessary. Smaller doses than those recommended above should not be used. Even higher doses may be needed at times. In stubborn infections, therapy may be required for several weeks. It may be necessary to continue clinical and/or bacteriological follow-up for several months after cessation of therapy.

Treatment should be continued for a minimum of 48 to 72 hours beyond the time that the patient becomes asymptomatic or evidence of bacterial eradication has been obtained. It is recommended that there be at least 10 days' treatment for any infection caused by hemolytic streptococci, to help prevent the occurrence of acute rheumatic fever or glomerulonephritis.

### **How Supplied**

Pen. A (ampicillin trihydrate) Capsules: Ampicillin trihydrate equivalent to 250 mg. or 500 mg. ampicillin per capsule.

250 mg.: bottles of 100 and 500.

500 mg.: bottles of 100.

Pen. A (ampicillin trihydrate) for Oral Suspension: Each 5 cc. of reconstituted suspension contains ampicillin trihydrate equivalent to 125 mg. or 250 mg. ampicillin.

125 mg./5 cc.: bottles of 100 cc. and 200 cc.

250 mg./5 cc.: bottles of 100 cc. and 200 cc.

**PFIZER LABORATORIES DIVISION**

**PFIZER INC.**

**NEW YORK, N.Y. 10017**

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**Approval Package for:**

**APPLICATION NUMBER:**

**60-666 supplement**

Trade Names: Totacillin, Alpen, and Pen A for Oral  
Suspension 125mg/5mL and  
250mg/5mL

Generic Name: ampicillin trihydrate

Sponsor: Beecham-Massengill

Approval Date: November 30, 1972

# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:**

**60-666 supplement**

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**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**APPROVAL LETTER**

A-6  
~~XXXXXXXXXX~~

# Beecham-Massengill Pharmaceuticals

DIV. OF BEECHAM INC. CLIFTON, NEW JERSEY

65 INDUSTRIAL SOUTH  
CLIFTON, NEW JERSEY 07012

CABLE ADDRESS "BEECHPROD"  
TELEX 133471

PHONES NEW JERSEY 201-778-9000  
TENNESSEE 615-764-5141

November 15, 1972

Date Approved 11/30/72

Food and Drug Administration  
Div. of Anti-Infective Drug Products  
Certifiable Drug Review Unit (BD-145)  
Bureau of Drugs  
5600 Fishers Lane  
Rockville, Maryland 20852

Account No. \_\_\_\_\_

Signed John D. Adams  
For the Commissioner of Food and Drugs  
Department of Health, Education and  
Welfare

Re: NDA # 60-666 (146a.118)

Gentlemen:

Reference is made to Beecham-Massengill Pharmaceuticals' approved Form 6 # 60-666 covering Ampicillin trihydrate for Oral Suspension.

We hereby wish to supplement our application to provide for up-dated manufacturing directions for ampicillin trihydrate for oral suspension, 125 mg./5 cc. and 250 mg./5 cc., distributed under the trade names; Totacillin, Alpen, and Pen A.

This supplement is submitted in triplicate.

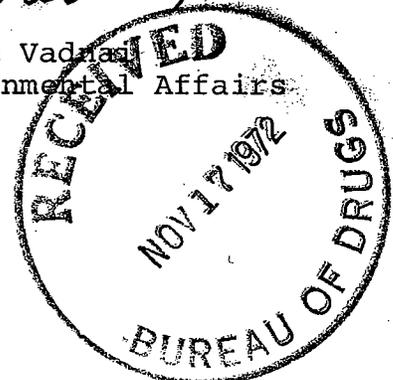


Sincerely,

BEECHAM-MASSENGILL PHARMACEUTICALS

G. Vadnos

George Vadnos  
Manager, Governmental Affairs



GSV:dmm

Enclosures

9098

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**Approval Package for:**

**APPLICATION NUMBER:**

**60-666 supplement**

Trade Name: Totacillin for Oral Suspension  
125mg/5mL and 250mg/5mL

Generic Name: ampicillin trihydrate

Sponsor: Beecham-Massengill Pharmaceuticals

Approval Date: March 4, 1975

# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:**

**60-666 supplement**

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Microbiology Review(s)	
Bioequivalence Review(s)	
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Correspondence	

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**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**APPROVAL LETTER**

11-6  
~~11-6~~

①

# Beecham-Massengill - Pharmaceuticals

DIVISION OF BEECHAM INC. CLIFTON, NEW JERSEY

**BMP**

65 INDUSTRIAL SOUTH  
CLIFTON, NEW JERSEY 07012  
REGULATORY DEPARTMENT

*OK to sign out  
JDF 3/4/75*

CABLE ADDRESS "BEECHPROD"  
TELEX 133471

PHONE: 201-778-9000

(For use of State and Federal Agencies)

Date received 3/4/75

Approved For: *JDF*

Signed: *JDF*

For use: *JDF*

Department of Health, Education, and Welfare

February 28, 1975.

Food and Drug Administration  
 Certifiable Drug Review Staff (HFD-535)  
 Div. of Generic Drug Monographs  
 Bureau of Drugs  
 5600 Fishers Lane  
 Rockville, Maryland 20852

Re: #60-666 (440.107c)

Gentlemen:

Reference is made to Beecham Laboratories' approved Form 6 Antibiotic Application for Ampicillin Trihydrate for Oral Suspension.

We hereby wish to supplement our Application to provide for final printed labeling which reflects the recent change in the Company name.

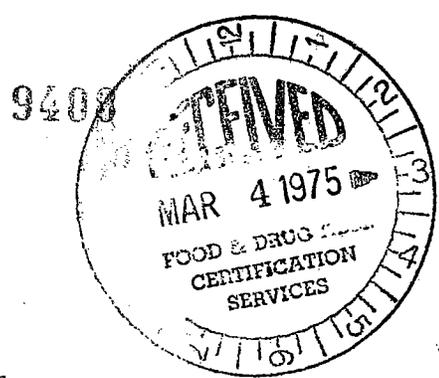
This supplement is submitted in triplicate.

Sincerely,

BEECHAM LABORATORIES

*J. Benta / G. Vadnai*

George Vadnai  
Manager, Governmental Affairs



GSV:dmm  
Enclosures

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**FINAL PRINTED LABELING**

Beecham  
laboratories

TO-D

**TOTACILLIN®**  
ampicillin

CAPSULES  
250 mg.  
and  
500 mg.

for  
ORAL SUSPENSION  
125 mg./5 ml.  
and  
250 mg./5 ml.

**DESCRIPTION**

TOTACILLIN (Ampicillin) is derived from the penicillin nucleus, 6-aminopenicillanic acid (6-APA), isolated by Beecham. Chemically it is D (-)- $\alpha$ -aminobenzyl penicillin trihydrate.

**ACTIONS**

**MICROBIOLOGY:**

TOTACILLIN (Ampicillin) is similar to benzyl penicillin in its bactericidal action against sensitive organisms during the stage of active multiplication. It acts through the inhibition of biosynthesis of cell wall mucopolysaccharide. TOTACILLIN (Ampicillin) differs in *in vitro* spectrum from benzyl penicillin in the Gram-negative spectrum. It exerts high *in vitro* activity against many strains of *Haemophilus influenzae*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Neisseria catarrhalis*, *Escherichia coli*, *Proteus mirabilis*, *Bacteroides funduliformis*, *Salmonellae* and *Shigellae*.

*In vitro* studies have also demonstrated the sensitivity of many strains of the following Gram-positive bacteria: alpha- and beta-hemolytic streptococci, *Diplococcus pneumoniae*, nonpenicillinase-producing staphylococci, *Bacillus anthracis*, and most strains of enterococci and clostridia. Ampicillin generally provides less *in vitro* activity than penicillin G against Gram-positive bacteria. Because it does not resist destruction by penicillinase, it is not effective against penicillinase-producing bacteria, particularly resistant staphylococci. All strains of *Pseudomonas* and most strains of *Klebsiella* and *Aerobacter* are resistant.

**PHARMACOLOGY:**

TOTACILLIN (Ampicillin) is acid stable and, therefore, well absorbed. Food, however, retards absorption. Blood serum levels of approximately 2 mcg./ml. are attained within 1-2 hours following a 250 mg. oral dose given to fasting adults. Detectable amounts persist for about 6 hours.

TOTACILLIN (Ampicillin) diffuses readily into all body tissues and fluids with the exception of brain and spinal fluid except when meninges are inflamed. Higher serum levels are obtained following I.M. injection. Most of the Ampicillin is excreted unchanged in the urine and this excretion can be delayed by concurrent administration of probenecid. The active form appears in the bile in higher concentrations than found in the serum. TOTACILLIN (Ampicillin) is one of the least serum bound of all the penicillins averaging about 20% compared to approximately 60%-90% for other penicillins.

**INDICATIONS**

TOTACILLIN (Ampicillin) is indicated in the treatment of infections due to susceptible strains of the following:

Gram-negative Organisms: *Shigellae*, *Salmonellae* (including *S. typhosa*), *H. influenzae*, *E. coli*, *P. mirabilis*, *N. gonorrhoeae*, and *N. meningitidis*.

Gram-positive Organisms: Streptococci, *D. pneumoniae*, and nonpenicillinase-producing staphylococci.

Because of its wide spectrum and bactericidal action, it may be useful in instituting therapy; however, bacteriological studies to determine the causative organisms and their sensitivity to Ampicillin should be performed. Indicated surgical procedures should be performed.

**CONTRAINDICATIONS**

The use of this drug is contraindicated in individuals with a history of an allergic reaction to any of the penicillins.

**WARNINGS**

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL THERAPY, IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. THESE REACTIONS ARE MORE APT TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR HYPERSENSITIVITY REACTIONS TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE THERAPY WITH A PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, THE DRUG SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE, OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

**USAGE IN PREGNANCY:**

Safety for use in pregnancy has not been established.

**PRECAUTIONS**

As with any antibiotic preparation, constant observation for signs of overgrowth of nonsusceptible organisms, including fungi, is essential. Should superinfection occur (usually involving *Aerobacter*, *Pseudomonas*, or *Candida*), the drug should be discontinued and/or appropriate therapy instituted. As with any potent agent, it is advisable to check periodically for organ system dysfunction during prolonged therapy; this includes renal, hepatic, and hematopoietic systems. This is particularly important in

following adverse reactions have been reported as associated with the use of Ampicillin:

**Gastrointestinal**—Glossitis, stomatitis, black "hairy" tongue, nausea, vomiting, and diarrhea. (These reactions are usually associated with oral dosage forms.)

**Hypersensitivity reactions**—An erythematous maculopapular rash has been reported fairly frequently. Urticaria and erythema multiforme have been reported occasionally. A few cases of exfoliative dermatitis have been reported. Anaphylaxis is the most serious reaction experienced and has usually been associated with the parenteral dosage form.

**Note:** Urticaria, other skin rashes, and serum sickness-like reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, Ampicillin should be discontinued unless, in the opinion of the physician, the condition being treated is life-threatening and amenable only to Ampicillin therapy.

**Liver**—A moderate rise in serum glutamic oxaloacetic transaminase (SGOT) has been noted, particularly in infants, but the significance of this finding is unknown.

**Hemic and Lymphatic Systems**—Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia, and agranulocytosis have been reported during therapy with the penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be sensitivity reactions.

#### DOSAGE AND ADMINISTRATION

*Infections of the ear, nose, throat, and lower respiratory tract due to streptococci, pneumococci, and nonpenicillinase-producing staphylococci, and also those infections of the upper and lower respiratory tract due to H. influenzae.*

ADULTS: 250 mg. every 6 hours  
CHILDREN: 50 mg./kg./day in divided doses every 6 or 8 hours.

*Infections of the genitourinary tract caused by sensitive Gram-negative and Gram-positive bacteria:*

ADULTS: 500 mg. every 6 hours. Larger doses may be required for severe infections.  
CHILDREN: 100 mg./kg./day in divided doses every 6 hours.

*Uncomplicated urethritis due to N. gonorrhoeae:*

ADULT MALES AND FEMALES: 3.5 grams single oral dose administered simultaneously with 1 gram of probenecid.

*Cases of gonorrhea with a suspected lesion of syphilis should have dark-field examinations before receiving Ampicillin, and monthly serological tests for a minimum of 4 months.*

*Infections of the gastrointestinal tract:*

ADULTS: 500 mg. every 6 hours.  
CHILDREN: 100 mg./kg./day in divided doses every 6 hours.

Larger doses may be required for stubborn or severe infections. The children's dosage is intended for individuals whose weight will not cause a dosage to be calculated greater than that recommended for adults. Children weighing more than 20 kg. should be dosed according to the adult recommendations.

It should be recognized that in the treatment of chronic urinary tract and intestinal infections, frequent bacteriological and clinical appraisals are necessary. Smaller doses than those recommended above should not be used. Even higher doses may be needed at times. In stubborn infections, therapy may be required for several weeks. It may be necessary to continue clinical and/or bacteriological follow-up for several months after cessation of therapy.

Treatment should be continued for a minimum of 48 to 72 hours beyond the time that the patient becomes asymptomatic or evidence of bacterial eradication has been obtained. It is recommended that there be at least 10 days' treatment for any infection caused by hemolytic streptococci to help prevent the occurrence of acute rheumatic fever or glomerulonephritis.

#### DIRECTIONS FOR MIXING ORAL SUSPENSION

Prepare suspension at time of dispensing as follows: Add the required amount of water (see table below) to the bottle. For ease of preparation, add water in two portions. Shake well after each addition of water. Each teaspoonful (5 ml.) will contain 125 mg. or 250 mg. Ampicillin.

Bottle Size	Amount of Water Required for Reconstitution
80 ml.	53 ml.
100 ml.	66 ml.
150 ml.	100 ml.
200 ml.	132 ml.

SHAKE WELL BEFORE USING. Keep bottle tightly closed. Any unused portion of the reconstituted suspension must be discarded after 7 days at room temperature or 14 days under refrigeration.

#### HOW SUPPLIED

**TOTACILLIN (Ampicillin) Capsules.** Each capsule contains 250 mg. or 500 mg. Ampicillin as the trihydrate.

250 mg./Capsule		500 mg./Capsule	
NDC 0029-6615-30	... bottles of 100	NDC 0029-6620-29	... bottles of 50
NDC 0029-6615-32	... bottles of 500	NDC 0029-6620-32	... bottles of 500
NDC 0029-6615-31	... unit dose cartons of 100	NDC 0029-6620-31	... unit dose cartons of 100

**TOTACILLIN (Ampicillin) for Oral Suspension.** Each 5 ml. of reconstituted suspension contains 125 mg. or 250 mg. Ampicillin as the trihydrate.

125 mg./5 ml.		250 mg./5 ml.	
NDC 0029-6625-21	... 80 ml. bottle	NDC 0029-6630-21	... 80 ml. bottle
NDC 0029-6625-23	... 100 ml. bottle	NDC 0029-6630-23	... 100 ml. bottle
NDC 0029-6625-22	... 150 ml. bottle	NDC 0029-6630-22	... 150 ml. bottle
NDC 0029-6625-24	... 200 ml. bottle	NDC 0029-6630-24	... 200 ml. bottle

**KEEP TIGHTLY CLOSED • SHAKE WELL BEFORE USING**  
Any unused portion of the reconstituted suspension must be discarded after 7 days at room temperature or 14 days under refrigeration.

Control No.  
Exp. Date

See along perforation

BEECHAM LABORATORIES

DIV. OF BEECHAM INC. BRISTOL, TENN. 37620

**STORE DRY POWDER AT ROOM TEMPERATURE**

**CAUTION:** Federal law prohibits dispensing without prescription.

NDC 0029-6625-23  
**TOTACILLIN®**  
ampicillin  
for oral suspension

Equivalent to  
2.5 Gm. Ampicillin  
When reconstituted  
each 5 ml. will contain

**125 mg.**

Ampicillin as the trihydrate  
100 ml.

**Beecham**  
laboratories

**DIRECTIONS FOR MIXING:**

Add a total of 66 ml. of water to the bottle. For ease of preparation, add water in two portions. Shake well after each addition of water. Each 5 ml. (1 teaspoonful) will then contain Ampicillin Trihydrate equivalent to 125 mg. Ampicillin.

**USUAL DOSAGE:**

Children: 50-100 mg./kg./day in divided doses every 6-8 hours.  
Adults: 250-500 mg. every 6 hours.

**READ ACCOMPANYING INSERT BEFORE USE** 6446/B

**KEEP TIGHTLY CLOSED • SHAKE WELL BEFORE USING**  
Any unused portion of the reconstituted suspension must be discarded after 7 days at room temperature or 14 days under refrigeration.

Control No.  
Exp. Date

See along perforation

BEECHAM LABORATORIES

DIV. OF BEECHAM INC. BRISTOL, TENN. 37620

**STORE DRY POWDER AT ROOM TEMPERATURE**

**CAUTION:** Federal law prohibits dispensing without prescription.

NDC 0029-6625-21  
**TOTACILLIN®**  
ampicillin  
for oral suspension

Equivalent to  
2.0 Gm. Ampicillin  
When reconstituted  
each 5 ml. will contain

**125 mg.**

Ampicillin as the trihydrate

80 ml.

**Beecham**  
laboratories

**DIRECTIONS FOR MIXING:**

Add a total of 63 ml. of water to the bottle. For ease of preparation, add water in two portions. Shake well after each addition of water. Each 5 ml. (1 teaspoonful) will then contain Ampicillin Trihydrate equivalent to 125 mg. Ampicillin.

**USUAL DOSAGE:**

Children: 50-100 mg./kg./day in divided doses every 6-8 hours.  
Adults: 250-500 mg. every 6 hours.

**READ ACCOMPANYING INSERT BEFORE USE** 6306/B

**KEEP TIGHTLY CLOSED • SHAKE WELL BEFORE USING**  
Any unused portion of the reconstituted suspension must be discarded after 7 days at room temperature or 14 days under refrigeration.

Control No. \_\_\_\_\_  
Exp. Date \_\_\_\_\_

Tear along perforation

**BEECHAM LABORATORIES**  
DIV. OF BEECHAM INC. BRISTOL, TENN. 37620

**STORE DRY POWDER AT ROOM TEMPERATURE**  
**CAUTION:** Federal law prohibits dispensing without prescription.

NDC 0029-6625-22

**TOTACILLIN®**  
ampicillin

for oral suspension

Equivalent to  
3.75 Gm. Ampicillin

When reconstituted  
each 5 ml. will contain

**125 mg.**

Ampicillin as the trihydrate

**150 ml.**

**Beecham**  
laboratories

**DIRECTIONS FOR MIXING:**  
Add a total of 100 ml. of water to the bottle. For ease of preparation, add water in two portions. Shake well after each addition of water. Each 5 ml. (1 teaspoonful) will then contain Ampicillin Trihydrate equivalent to 125 mg. Ampicillin.

**USUAL DOSAGE:**  
Children: 50-100 mg./kg./day in divided doses every 6-8 hours.  
Adults: 250-500 mg. every 6 hours.

**READ ACCOMPANYING INSERT BEFORE USE** 6309/C

**KEEP TIGHTLY CLOSED • SHAKE WELL BEFORE USING**  
Any unused portion of the reconstituted suspension must be discarded after 7 days at room temperature or 14 days under refrigeration.

Control No. \_\_\_\_\_  
Exp. Date \_\_\_\_\_

Tear along perforation

**BEECHAM LABORATORIES**  
DIV. OF BEECHAM INC. BRISTOL, TENN. 37620

**STORE DRY POWDER AT ROOM TEMPERATURE**  
**CAUTION:** Federal law prohibits dispensing without prescription.

NDC 0029-6625-24

**TOTACILLIN®**  
ampicillin

for oral suspension

Equivalent to  
5.0 Gm. Ampicillin

When reconstituted  
each 5 ml. will contain

**125 mg.**

Ampicillin as the trihydrate

**200 ml.**

**Beecham**  
laboratories

**DIRECTIONS FOR MIXING:**  
Add a total of 132 ml. of water to the bottle. For ease of preparation, add water in two portions. Shake well after each addition of water. Each 5 ml. (1 teaspoonful) will then contain Ampicillin Trihydrate equivalent to 125 mg. Ampicillin.

**USUAL DOSAGE:**  
Children: 50-100 mg./kg./day in divided doses every 6-8 hours.  
Adults: 250-500 mg. every 6 hours.

**READ ACCOMPANYING INSERT BEFORE USE** 6447/B

**KEEP TIGHTLY CLOSED • SHAKE WELL BEFORE USING**  
Any unused portion of the reconstituted suspension must be discarded after 7 days at room temperature or 14 days under refrigeration.

Control No. \_\_\_\_\_  
Exp. Date \_\_\_\_\_

Tear along perforation

**BEECHAM LABORATORIES**  
DIV. OF BEECHAM INC. BRISTOL, TENN. 37620

**STORE DRY POWDER AT ROOM TEMPERATURE**

**CAUTION:** Federal law prohibits dispensing without prescription.

NDC 0029-6630-21  
**TOTACILLIN®**  
ampicillin  
for oral suspension

Equivalent to  
4.0 Gm. Ampicillin  
When reconstituted  
each 5 ml. will contain

**250 mg.**

Ampicillin as the trihydrate

**80 ml.**

**Beecham**  
laboratories

**DIRECTIONS FOR MIXING:**  
Add a total of 53 ml. of water to the bottle. For ease of preparation, add water in two portions. Shake well after each addition of water. Each 5 ml. (1 teaspoonful) will then contain Ampicillin Trihydrate equivalent to 250 mg. Ampicillin.

**USUAL DOSAGE:**  
Children: 50-100 mg./kg./day in divided doses every 6-8 hours.  
Adults: 250-500 mg. every 6 hours.

**READ ACCOMPANYING INSERT BEFORE USE** 6312/B

**KEEP TIGHTLY CLOSED • SHAKE WELL BEFORE USING**  
Any unused portion of the reconstituted suspension must be discarded after 7 days at room temperature or 14 days under refrigeration.

Control No. \_\_\_\_\_  
Exp. Date \_\_\_\_\_

Tear along perforation

**BEECHAM LABORATORIES**  
DIV. OF BEECHAM INC. BRISTOL, TENN. 37620

**STORE DRY POWDER AT ROOM TEMPERATURE**

**CAUTION:** Federal law prohibits dispensing without prescription.

NDC 0029-6630-23  
**TOTACILLIN®**  
ampicillin  
for oral suspension

Equivalent to  
5.0 Gm. Ampicillin  
When reconstituted  
each 5 ml. will contain

**250 mg.**

Ampicillin as the trihydrate

**100 ml.**

**Beecham**  
laboratories

**DIRECTIONS FOR MIXING:**  
Add a total of 66 ml. of water to the bottle. For ease of preparation, add water in two portions. Shake well after each addition of water. Each 5 ml. (1 teaspoonful) will then contain Ampicillin Trihydrate equivalent to 250 mg. Ampicillin.

**USUAL DOSAGE:**  
Children: 50-100 mg./kg./day in divided doses every 6-8 hours.  
Adults: 250-500 mg. every 6 hours.

**READ ACCOMPANYING INSERT BEFORE USE** 6448/B

**KEEP TIGHTLY CLOSED • SHAKE WELL BEFORE USING**  
Any unused portion of the reconstituted suspension must be discarded after 7 days at room temperature or 14 days under refrigeration.

Control No.

Exp. Date

Tear along perforation

BEECHAM LABORATORIES  
DIV. OF BEECHAM INC. BOSTON, MASS. 02120

STORE DRY POWDER AT ROOM TEMPERATURE

CAUTION: Federal law prohibits dispensing without prescription.

NDC 0029-6630-22

## TOTACILLIN® ampicillin

for oral suspension

Equivalent to  
7.50 Gm. Ampicillin  
When reconstituted  
each 5 ml. will contain

**250 mg.**

Ampicillin as the trihydrate

**150 ml.**

**Beecham**  
laboratories

**DIRECTIONS FOR MIXING:**  
Add a total of 100 ml. of water to the bottle. For ease of preparation, add water in two portions. Shake well after each addition of water. Each 5 ml. (1 teaspoonful) will then contain Ampicillin Trihydrate equivalent to 250 mg. Ampicillin.

**USUAL DOSAGE:**  
Children: 50-100 mg./kg./day in divided doses every 6-8 hours.  
Adults: 250-500 mg. every 6 hours.

**READ ACCOMPANYING INSERT BEFORE USE** 6315/C

**KEEP TIGHTLY CLOSED • SHAKE WELL BEFORE USING**  
Any unused portion of the reconstituted suspension must be discarded after 7 days at room temperature or 14 days under refrigeration.

Control No.

Exp. Date

Tear along perforation

BEECHAM LABORATORIES  
DIV. OF BEECHAM INC. BOSTON, MASS. 02120

STORE DRY POWDER AT ROOM TEMPERATURE

CAUTION: Federal law prohibits dispensing without prescription.

NDC 0029-6630-24

## TOTACILLIN® ampicillin

for oral suspension

Equivalent to  
10.0 Gm. Ampicillin

When reconstituted  
each 5 ml. will contain

**250 mg.**

Ampicillin as the trihydrate

**200 ml.**

**Beecham**  
laboratories

**DIRECTIONS FOR MIXING:**  
Add a total of 132 ml. of water to the bottle. For ease of preparation, add water in two portions. Shake well after each addition of water. Each 5 ml. (1 teaspoonful) will then contain Ampicillin Trihydrate equivalent to 250 mg. Ampicillin.

**USUAL DOSAGE:**  
Children: 50-100 mg./kg./day in divided doses every 6-8 hours.  
Adults: 250-500 mg. every 6 hours.

**READ ACCOMPANYING INSERT BEFORE USE** 6449/B

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**Approval Package for:**

**APPLICATION NUMBER:**

**60-666 supplement**

Trade Name: Penbritin for Oral Suspension  
125mg/5mL and 250mg/5mL

Generic Name: ampicillin trihydrate

Sponsor: Beecham Laboratories

Approval Date: April 14, 1975

# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:**

**60-666 supplement**

## CONTENTS

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### Reviews / Information Included in this ANDA Review.

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Approval Letter(s)	X
Tentative Approval Letter(s)	
Final Printed Labeling	X
CSO Labeling Review(s)	
Medical Officer Review(s)	
Chemistry Review(s)	
Microbiology Review(s)	
Bioequivalence Review(s)	
Administrative Document(s)	
Correspondence	

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**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**APPROVAL LETTER**

①

H-6  
~~Powers~~

# Beecham laboratories

65 INDUSTRIAL SOUTH, CLIFTON, NEW JERSEY 07012 201-778-9000

REGULATORY DEPARTMENT

CABLE ADDRESS "BEECHPROD"  
TELEX 133471

*OK to sign out  
JDD 4/14/75*

April 8, 1975

Food and Drug Administration  
Certifiable Drug Review Staff (HFD-20505) No.  
Div. of Generic Drug Monographs  
Bureau of Drugs  
5600 Fishers Lane  
Rockville, Maryland 20852

(For use of Food and Drug Administration)	
Date approved	<u>4/14/75</u>
Signed	<u>John O. Lewis</u>
For the Commissioner of Food and Drugs Food and Drug Administration Department of Health, Education, and Welfare	

Re: #60-666 (440.107c)

Gentlemen:

Reference is made to Beecham Laboratories' approved Form 6 Antibiotic Application #60-666 covering Ampicillin for Oral Suspension, distributed by Ayerst Laboratories Inc. under the trade name Penbritin.

We are hereby submitting, in triplicate, a final printed package insert which is identical to the currently approved insert, except for the addition of the manufacturer's identification.

Sincerely,

BEECHAM LABORATORIES

*G. Vadnai*

George Vadnai  
Manager, Governmental Affairs

GSV:dmm

Enclosures

10136



**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**FINAL PRINTED LABELING**

# PENBRITIN\*

(ampicillin)

for  
**ORAL SUSPENSION**  
 125 mg./5 cc.  
 and  
 250 mg./5 cc.

**PEDIATRIC DROPS**  
 for  
**ORAL SUSPENSION**  
 100 mg./cc.

**CAUTION:** Federal law prohibits dispensing without prescription.

## DESCRIPTION

Chemical name: D(-)-alpha-aminobenzyl penicillin

PENBRITIN is an orally active, semisynthetic broad spectrum penicillin. It is inactivated by penicillinase.

## ACTIONS

Microbiologic:

Ampicillin appears to act primarily by interfering with the synthesis or maintenance of the bacterial cell wall. It strongly inhibits the early lag and logarithmic phases of bacterial multiplication. In *in vitro* studies, ampicillin is bactericidal.

PENBRITIN is effective against the usual penicillin-susceptible gram-positive organisms, and in addition, many gram-negative pathogens. It is active *in vitro* against many strains of the following bacteria:

**GRAM-POSITIVE**— Alpha and beta hemolytic streptococci, nonpenicillinase-producing staphylococci, *Diplococcus pneumoniae*, *Clostridia* species, *Bacillus anthracis*, most strains of enterococci.

**GRAM-NEGATIVE**— *Haemophilus influenzae*, *Neisseria gonorrhoeae* and meningitidis, *Proteus mirabilis*, *Escherichia coli*, *Salmonella* (including *S. typhosa*), *Neisseria catarrhalis*, *Bacteroides funduliformis*, and *Shigella*.

All strains of *Pseudomonas* and most strains of *Klebsiella-Aerobacter* are resistant. Because ampicillin is destroyed by penicillinase, PENBRITIN is not effective against penicillinase-producing bacteria.

Pharmacologic:

PENBRITIN is stable in acid and is therefore not destroyed by gastric juice. (Food, however, retards absorption.) PENBRITIN is well absorbed and produces high and persistent blood levels of unbound ampicillin. Ampicillin is the least protein bound of all the penicillins, averaging 20 percent as contrasted with 60 to 90 percent for the others. Blood serum levels of approximately 2 mcg./ml. are achieved within one to two hours following a 250 mg. oral dose to fasting adults. Detectable amounts persist in the blood for about six hours. There are high concentrations in the bile and urine. Ampicillin diffuses readily into most body tissues and fluids. However, penetration into the cerebral spinal fluid occurs only with meningeal inflammation. Ampicillin is excreted in the urine, largely unchanged, and this excretion can be delayed by concurrent administration of probenecid.

## INDICATIONS

PENBRITIN is indicated in the treatment of infections due to susceptible strains of the following:

**GRAM-NEGATIVE** organisms: *Shigella*, *Salmonella* (including *S. typhosa*), *H. influenzae*, *E. coli*, *P. mirabilis*, *N. gonorrhoeae*, and *N. meningitidis*.

**GRAM-POSITIVE** organisms: Streptococci, nonpenicillinase-producing staphylococci, and *D. pneumoniae*.

Bacteriologic studies to determine the causative organisms and their sensitivity to ampicillin should be performed. Because PENBRITIN is a broad spectrum antibiotic, therapy may be instituted prior to the results of sensitivity testing.

## CONTRAINDICATIONS

PENBRITIN is contraindicated in patients with a history of hypersensitivity to any penicillin.

## WARNINGS

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL THERAPY, IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. THESE REACTIONS ARE MORE APT TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR HYPERSENSITIVITY REACTIONS TO MULTIPLE ALLERGENS.

THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE THERAPY WITH A PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, AND OTHER ALLERGENS.

IF AN ALLERGIC REACTION OCCURS, THE DRUG SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE, OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

USAGE IN PREGNANCY: Safety for use in pregnancy has not been established.

## PRECAUTIONS

As with any antibiotic preparation, constant observation for signs of overgrowth of nonsusceptible organisms, including fungi, is essential. Should superinfection occur (usually involving *Aerobacter*, *Pseudomonas*, or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.

Periodic assessment of renal, hepatic, and hematopoietic function should be made during prolonged therapy. This is particularly important in prematures, neonates and other infants.

## ADVERSE REACTIONS

As with other penicillins, it may be expected that untoward reactions will be essentially limited to sensitivity phenomena. These are more likely to occur in individuals with a history of allergy, asthma, hay fever, or urticaria.

The following adverse reactions have been reported as associated with the use of ampicillin:

Gastrointestinal— glossitis, stomatitis, black "hairy" tongue, nausea, vomiting, diarrhea. (These reactions are usually associated with oral administration.)

# PENBRITIN (ampicillin) for Oral Suspension & Pediatric Drops for Oral Suspension cont'd.

Hypersensitivity reactions — erythematous maculopapular rashes have been reported fairly frequently; urticaria, erythema multiforme, and an occasional case of exfoliative dermatitis have been reported. Anaphylaxis is usually associated with parenteral administration.

*Note:* Urticaria, other skin rashes, and serum sickness-like reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, ampicillin should be discontinued unless, in the opinion of the physician, the condition being treated is life-threatening and amenable only to ampicillin therapy.

Hepatic — A moderate rise in serum glutamic oxaloacetic transaminase (SGOT) has been noted, particularly in infants. The significance of this finding is unknown.

Hemic and lymphatic — anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia, and agranulocytosis have been reported. These are usually reversible on discontinuation of the drug, and are believed to be hypersensitivity phenomena.

## DOSAGE AND ADMINISTRATION

Infection	Usual Dosage* Adults	Usual Dosage* Children†
Respiratory tract	250 mg. q. 6 h.	50 mg./kg./day in equal doses q. 6-8 h.
Gastrointestinal tract Genitourinary tract	500 mg. q. 6 h.	100 mg./kg./day in equal doses q. 6-8 h.
Urethritis in Males or Females due to <i>N. gonorrhoeae</i>	3.5 Gm. single oral dose administered simultaneously with 1.0 Gm. of probenecid  In the treatment of complications of gonorrheal urethritis, such as prostatitis and epididymitis, prolonged and intensive therapy is recommended.  Cases of gonorrhea with a suspected primary lesion of syphilis should have dark-field examinations before receiving treatment. In all other cases where concomitant syphilis is suspected, monthly serologic tests should be made for a minimum of four months.	

\* Larger than usual dosages may be required for stubborn or severe infections. Smaller doses than those recommended above should not be used.

† The children's dosage is intended for individuals whose weight will not cause a dosage to be calculated greater than that recommended for adults. Children weighing more than 20 kg. (44 lb.) should be given the adult recommended dosage.

## PEDIATRIC DROPS:

A suggested dosage regimen is:  
Under 12 lb. — 0.6 cc. q. 6 hours.  
12-25 lb. — 1.0 cc. q. 6 hours.  
25-44 lb. — 2.0 cc. q. 6 hours.

**DURATION OF TREATMENT:** Medications should be continued for at least 48 to 72 hours after all symptoms have subsided or cultures have become negative. For any infection caused by hemolytic streptococci, at least 10 days of treatment is recommended to help prevent the occurrence of acute rheumatic fever or glomerulonephritis.

## DIRECTIONS FOR MIXING ORAL SUSPENSIONS

Prepare suspensions at time of dispensing as follows: Add the required amount of water (see table below) to the bottle and shake vigorously. Each teaspoonful (5 cc.) of reconstituted Oral Suspension will contain 125 mg. or 250 mg. ampicillin, depending upon the initial concentration. Each cc. of reconstituted Pediatric Drops will contain 100 mg. ampicillin.

Bottle Size	Amount of Water Required for Reconstitution
100 cc. Oral Suspension	66 cc.
200 cc. Oral Suspension	132 cc.
20 cc. Pediatric Drops	11.5 cc.

SHAKE WELL BEFORE USING.

## STABILITY

**ORAL SUSPENSION:** No refrigeration required before mixing. After mixing, suspension may be kept at room temperature (70° F.) for 7 days or in a refrigerator (40° F.) for 14 days without significant loss of potency. KEEP TIGHTLY CLOSED.

**PEDIATRIC DROPS:** No refrigeration required before mixing. After mixing, suspension may be kept in a refrigerator for 14 days without significant loss of potency. KEEP TIGHTLY CLOSED.

## HOW SUPPLIED

**PENBRITIN (ampicillin) for Oral Suspension — when reconstituted:**

Each 5 cc. (one teaspoonful) contains 125 mg. ampicillin as the trihydrate. Bottles for 100 cc. (NDC 0046-0607-86) and 200 cc. (NDC 0046-0607-82).

Each individual-dose sealed envelope provides a single dose of ampicillin anhydrous equivalent to 125 mg. ampicillin. Packages of 40 (NDC 0046-0607-40).

Each 5 cc. (one teaspoonful) contains 250 mg. ampicillin as the trihydrate. Bottles for 100 cc. (NDC 0046-0611-86) and 200 cc. (NDC 0046-0611-82).

Each individual-dose sealed envelope provides a single dose of ampicillin anhydrous equivalent to 250 mg. ampicillin. Packages of 40 (NDC 0046-0611-40).

**PENBRITIN (ampicillin) PEDIATRIC DROPS for Oral Suspension — when reconstituted:**

Each cc. contains 100 mg. ampicillin as the trihydrate. Bottles for 20 cc. (NDC 0046-0625-20).  
Manufactured by Beecham Laboratories, Div. of Beecham Inc., Bristol, Tenn. 37620

Distributed by  
**AYERST LABORATORIES INCORPORATED**  
New York, N.Y. 10017

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**Approval Package for:**

**APPLICATION NUMBER:**

**60-666 supplement**

Trade Name: Penbritin for Oral Suspension  
125mg/5mL and 250mg/5mL

Generic Name: ampicillin trihydrate

Sponsor: Beecham-Massengill Pharmaceuticals

Approval Date: June 21, 1973

# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:**

**60-666 supplement**

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**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**APPROVAL LETTER**

60-666 GEN  
~~Admission~~

# Beecham-Massengill Pharmaceuticals

65 INDUSTRIAL SOUTH  
CLIFTON, NEW JERSEY 07012

DIV. OF BEECHAM INC. CLIFTON, NEW JERSEY

CABLE ADDRESS "BEECHPROD"  
TELEX 133471

PHONES NEW JERSEY 201-778-9000  
TENNESSEE 615-764-5141

June 5, 1973

Date 6/21/73

Account No. \_\_\_\_\_

Signed John D. Cannon  
For the Commissioner of Food and Drugs  
Department of Health, Education and  
Welfare

Food and Drug Administration  
Bureau of Drugs  
Certifiable Drug Review Unit (BD-145)  
Anti-Infective Drug Products Division  
5600 Fishers Lane  
Rockville, Maryland 20852

Re: Ampicillin Trihydrate for  
Pediatric Drops

Gentlemen:

By this letter, we authorize the Administration to refer to and incorporate all information contained in Beecham-Massengill Pharmaceuticals' Master Files DMF \_\_\_\_\_, DMF \_\_\_\_\_ and Form 6 #60-666 into the Form 6 Application for Penbritin (ampicillin trihydrate) for Pediatric Drops, 100 mg./cc., sponsored by Ayerst Laboratories, New York, N.Y.



Sincerely yours,

BEECHAM-MASSENGILL PHARMACEUTICALS

G. Vadnai

George Vadnai  
Manager, Governmental Affairs

GSV:dmm

cc: Mr. J. Barbieri, Ayerst Labs.



1960

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**Approval Package for:**

**APPLICATION NUMBER:**

**60-666 supplement**

Trade Name: Penbritin for Oral Suspension  
125mg/5mL and 250mg/5mL

Generic Name: ampicillin trihydrate

Sponsor: Beecham-Massengill Pharmaceuticals

Approval Date: January 7, 1974

# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:**

**60-666 supplement**

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**CENTER FOR DRUG  
EVALUATION AND  
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**APPLICATION NUMBER:**

**60-666 supplement**

**APPROVAL LETTER**

# Beecham-Massengill Pharmaceuticals

A-6  
EIS/ER.

DIVISION OF BEECHAM INC. CLIFTON, NEW JERSEY

**BMP**

*Handwritten notes:*  
Beecham  
Jan 21 1974  
JMR

CABLE ADDRESS "BEECHPROD"  
TELEX 133471

PHONE: 201-778-9000

65 INDUSTRIAL SOUTH  
CLIFTON, NEW JERSEY 07012  
REGULATORY DEPARTMENT

December 19, 1973

Date Approved 1/7/74

Account No. \_\_\_\_\_

Signed John D. Harms  
For The Commissioner of Food and Drugs  
Department of Health, Education and  
Welfare

Food and Drug Administration  
Div. of Anti-Infective Drug Products  
Certifiable Drug Review Staff (HFD-145)  
Bureau of Drugs  
5600 Fishers Lane  
Rockville, Maryland 20852

Re: #60-666

Gentlemen:

Reference is made to Beecham-Massengill Pharmaceuticals' approved Form 6 Antibiotic Application for Ampicillin Trihydrate for Oral Suspension. We hereby wish to supplement our Application to provide 18 months stability data for the 6 initial pilot batches on which the formula change in 1972 was based.

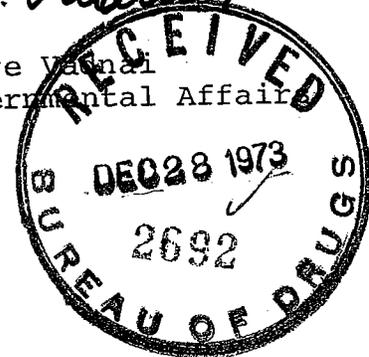
In addition, we are transmitting 6-8 months stability data for production size batches.

Sincerely,

BEECHAM-MASSENGILL PHARMACEUTICALS

*Handwritten signature:* G. Vadner

George Vadner  
Manager, Governmental Affairs



GSV:dmm

Enclosures

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**CORRESPONDENCE**

January 7, 1974

Our reference:  
60-666 (146a.118)

George Vadnai  
Manager, Governmental Affairs  
Beecham-Massengill Pharmaceuticals  
65 Industrial South  
Clifton, New Jersey 07012

Dear Mr. Vadnai:

This will acknowledge receipt of your letter of December 19, 1973 with which you furnished stability data for the revised formulation of your Ampicillin Trihydrate for Oral Suspension, 125 mg/5 ml. and 250 mg./5 ml.

The data appear to be satisfactory and will be added to the Form 6 file for this product.

A signed copy is enclosed for your files.

Sincerely yours,

Milton Eisler  
Certifiable Drug Review Staff (HFD-145)  
Division of Anti-Infective Drug Products

Enclosure

cc: NWK-DO  
HFD- 145  
HFD- 145/OD  
HFD- 430/lab.  
MEisler:hb

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**Approval Package for:**

**APPLICATION NUMBER:**

**60-666 supplement**

Trade Name: Totacillin, Alpen, and Pen A for Oral  
Suspension 125mg/5mL and  
250mg/5mL

Generic Name: ampicillin trihydrate

Sponsor: Beecham-Massengill Pharmaceuticals

Approval Date: May 30, 1974

# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:**

**60-666 supplement**

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**CENTER FOR DRUG  
EVALUATION AND  
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**APPLICATION NUMBER:**

**60-666 supplement**

**APPROVAL LETTER**

# Beecham-Massengill Pharmaceuticals

b-11

DIVISION OF BEECHAM INC. CLIFTON, NEW JERSEY

**BMP**

65 INDUSTRIAL SOUTH  
CLIFTON, NEW JERSEY 07012  
REGULATORY DEPARTMENT

CABLE ADDRESS "BEECHPROD"  
TELEX 133471

PHONE: 201-778-9000

May 24, 1974

Date Approved 5/30/74

Food and Drug Administration  
Div. of Anti-Infective Drug Products  
Certifiable Drug Review Unit (HFD-145)  
Bureau of Drugs  
5600 Fishers Lane  
Rockville, Maryland 20852

Account No. \_\_\_\_\_  
Signed John D. ...  
FOR THE ATTORNEY GENERAL  
Department of Health, Education and  
Welfare

Re: #60-666 (149b.15)

Gentlemen:

Reference is made to Beecham-Massengill Pharmaceuticals' approved Form 6 Antibiotic Application for Ampicillin for Oral Suspension (Totacillin, Alpen, Pen A). We hereby wish to supplement our Application to provide for the child-resistant safety closure required by the Poison Prevention Packaging Act. The following information is enclosed:

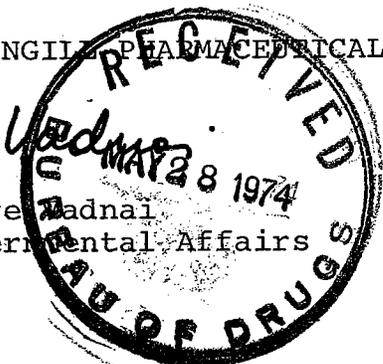
1. Specifications for the      safety closure used for the Ampicillin for Oral Suspension packages. The      which could be in contact with the drug is identical to the liner used with the metal caps utilized prior to the April 16 implementation of the Regulations.
2. Accelerated and short-term, comparative stability data for the safety closure. The long-term stability testing is continuing, and periodic reports will be submitted as the data becomes available.

This supplement is submitted in triplicate.

Sincerely,

BEECHAM-MASSENGILL PHARMACEUTICALS

George Madnai  
Manager, Governmental Affairs



GSV:dmm  
Enclosures

5191

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**Approval Package for:**

**APPLICATION NUMBER:**

**60-666 supplement**

Trade Name: Alpen for Oral Suspension  
125mg/5mL and 250mg/5mL

Generic Name: ampicillin trihydrate

Sponsor: Beecham-Massengill Pharmaceuticals

Approval Date: June 24, 1974

# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:**

**60-666 supplement**

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**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**APPROVAL LETTER**

①  
*Beecham-Massengill Pharmaceuticals*

DIVISION OF BEECHAM INC. CLIFTON, NEW JERSEY

6-~~8~~

65 INDUSTRIAL SOUTH  
CLIFTON, NEW JERSEY 07012  
REGULATORY DEPARTMENT

**BMP**

CABLE ADDRESS "BEECHPROD"  
TELEX 133471

PHONE: 201-778-9000

*OK to sign out  
JEP 6/24/74*

June 19, 1974

Food and Drug Administration  
Div. of Anti-Infective Drug Products  
Certifiable Drug Review Staff (HFD-145)  
Bureau of Drugs  
5600 Fishers Lane  
Rockville, Maryland 20852

(For use of Food and Drug Administration)
Date approved: <u>6/24/74</u>
Approved by: <i>John D. Hansen</i>
For use of: <u>Food and Drug Administration</u>
Department of: <u>Health, Education, and Welfare</u>

Re: #60-666 (440.107c)

Gentlemen:

Reference is made to Beecham-Massengill Pharmaceuticals' approved Form 6 #60-666, covering Ampicillin Trihydrate for Oral Suspension, distributed by Lederle Laboratories under the trade name Alpen.

We are submitting, in triplicate, final printed labeling which reflects the labeling changes required by the revised Ampicillin Regulations.

Sincerely,

BEECHAM-MASSENGILL PHARMACEUTICALS

*George Vadnai*

George Vadnai  
Manager, Governmental Affairs

GSV:dmm

Enclosures



5546 ✓

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**FINAL PRINTED LABELING**

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**FINAL PRINTED LABELING**

# ALPEN\*

## AMPICILLIN

### for Oral Use

#### DESCRIPTION

ALPEN *ampicillin* is derived from the penicillin nucleus, 6-aminopenicillanic acid (6-APA). Chemically it is D (-)  $\alpha$ -aminobenzylpenicillin trihydrate.

#### ACTIONS

##### MICROBIOLOGY:

Ampicillin is similar to benzyl penicillin in its bactericidal action against sensitive organisms during the stage of active multiplication. It acts through the inhibition of biosynthesis of cell wall mucopolysaccharide. Ampicillin differs in *in vitro* spectrum from benzylpenicillin in the Gram-negative spectrum. It exerts high *in vitro* activity against many strains of *Hemophilus influenzae*, *Neisseria gonorrhoeae*, *Neisseria meningitidis* and *Neisseria catarrhalis*, *Escherichia coli*, *Proteus mirabilis*, *Bacteroides funduliformis*, *Salmonellae*, and *Shigellae*.

*In vitro* studies have also demonstrated the sensitivity of many strains of the following Gram-positive bacteria: alpha- and beta-hemolytic streptococci, *Diplococcus pneumoniae*, nonpenicillinase-producing staphylococci, *Bacillus anthracis*, and most strains of enterococci and clostridia. Ampicillin generally provides less *in vitro* activity than penicillin-G against Gram-positive bacteria. Because it does not resist destruction by penicillinase it is not effective against penicillinase-producing bacteria, particularly resistant staphylococci. All strains of *Pseudomonas* and most strains of *Klebsiella* and *Aerobacter* are resistant.

##### PHARMACOLOGY:

ALPEN *ampicillin* is acid stable and, therefore, well absorbed. Food, however, retards absorption. Blood serum levels of approximately 2 mcg./ml. are attained within 1-2 hours following a 250 mg. oral dose given to fasting adults. Detectable amounts persist for about 6 hours. Ampicillin diffuses readily into all body tissues and fluids with the exception of brain and spinal fluid except when meninges are inflamed. Higher serum levels are obtained following I.M. injection. Most of the ampicillin is excreted unchanged in the urine and this excretion can be delayed by concurrent administration of probenecid. The active form appears in the bile in higher concentrations than found in the serum. Ampicillin is least serum bound of all the penicillins, averaging about 20% compared to approximately 60%-90% for other penicillins.

##### INDICATIONS

ALPEN *ampicillin* is indicated in the treatment of infections due to susceptible strains of the following: **Gram-Negative Organisms** - *Shigellae*, *Salmonellae* (including *S. typhosa*), *H. influenzae*, *E. coli*, *P. mirabilis*, *N. gonorrhoeae* and *N. meningitidis*. **Gram-Positive Organisms** - Streptococci, *D. pneumoniae*, and nonpenicillinase-producing staphylococci.

Because of its wide spectrum and bactericidal action, it may be useful in instituting therapy; however, bacteriological studies to determine the causative organisms and their sensitivity to ampicillin should be performed.

Indicated surgical procedures should be performed.

##### CONTRAINDICATIONS

The use of this drug is contraindicated in individuals with a history of an allergic reaction to any of the penicillins.

##### WARNINGS

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL THERAPY IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. THESE REACTIONS ARE MORE APT TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR HYPERSENSITIVITY REACTIONS TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE THERAPY WITH A PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, THE DRUG SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE, OXYGEN, INTRAVENOUS STEROIDS, ANY AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

##### USAGE IN PREGNANCY:

Safety for use in pregnancy has not been established.

##### PRECAUTIONS

As with any antibiotic preparation, constant observations for signs of overgrowth of nonsusceptible organisms, including fungi, are essential. Should superinfection occur (usually involving *Aerobacter*, *Pseudomonas*, or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.

As with any potent agent, it is advisable to check periodically for organ system dysfunction during prolonged therapy; this includes renal, hepatic, and hematopoietic systems. This is particularly important in prematures, neonates and other infants.

##### ADVERSE REACTIONS

As with other penicillins, it may be expected that untoward reactions will be essentially limited to sensitivity phenomena. They are more likely to occur in individuals who have previously demonstrated hypersensitivity to penicillins and in those with a history of allergy, asthma, hay fever, or urticaria.

The following adverse reactions have been reported as associated with the use of ampicillin:

**Gastrointestinal** - Glossitis, stomatitis, black "hairy" tongue, nausea, vomiting, diarrhea. (These reactions are usually associated with oral dosage forms.)

**Hypersensitivity Reactions** — An erythematous maculopapular rash has been reported fairly frequently. Urticaria and erythema multiforme have been reported occasionally. A few cases of exfoliative dermatitis have been reported. Anaphylaxis is the most serious reaction experienced and has usually been associated with the parenteral dosage form.

**NOTE:**

Urticaria, other skin rashes, and serum sickness-like reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, ampicillin should be discontinued unless, in the opinion of the physician, the condition being treated is life-threatening and amenable only to ampicillin therapy.

**LIVER** — A moderate rise in serum glutamic oxaloacetic transaminase (SGOT) has been noted, particularly in infants, but the significance of this finding is unknown.

**HEMIC AND LYMPHATIC SYSTEMS** — Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia, and agranulocytosis have been reported during therapy with the penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be sensitivity reactions.

**DOSAGE**

*Infections of the ear, nose, throat, and lower respiratory tract due to streptococci, pneumococci, and nonpenicillinase-producing staphylococci; and also those infections of the upper and lower respiratory tract due to H. influenzae.*

Adults: 250 mg. every 6 hours.  
Children: 50 mg./kg./day in divided doses every 6 or 8 hours.

*Infections of the genitourinary tract caused by sensitive Gram-negative and Gram-positive bacteria.*

Adults: 500 mg. every 6 hours. Larger doses may be required for severe infections.  
Children: 100 mg./kg./day in divided doses every 6 hours.

*Uncomplicated urethritis due to N. gonorrhoeae.*

Adult males and females: 3.5 grams single oral dose administered simultaneously with 1.0 gram of probenecid.

*Cases of gonorrhea with a suspected lesion of syphilis should have dark-field examinations before receiving ampicillin, and monthly serological tests for a minimum of 4 months.*

*Infections of the gastrointestinal tract.*

Adults: 500 mg. every 6 hours.  
Children: 100 mg./kg./day in divided doses every 6 hours.

Larger doses may be required for stubborn or severe infections. The children's dosage is intended for individuals whose weight will not cause a dosage to be calculated greater than that recommended for adults. Children weighing more than 20 kg. should be dosed according to the adult recommendations.

It should be recognized that in the treatment of chronic urinary tract and intestinal infections, frequent bacteriological and clinical appraisals are necessary. Smaller doses than those recommended above should not be used. Even higher doses may be needed at times. In stubborn infections, therapy may be required for several weeks. It may be necessary to continue clinical and/or bacteriological follow-up for several months after cessation of therapy.

Treatment should be continued for a minimum of 48 to 72 hours beyond the time that the patient becomes asymptomatic or evidence of bacterial eradication has been obtained. It is recommended that there be at least 10 days' treatment for any infection caused by hemolytic streptococci, to help prevent the occurrence of acute rheumatic fever or glomerulonephritis.

**DIRECTIONS for MIXING ORAL SUSPENSION**

Prepare suspension at time of dispensing as follows: Add the required amount of water (see table below) to the bottle and shake vigorously. Each teaspoonful (5 cc.) will contain 125 mg. or 250 mg. ampicillin.

Bottle Size	Amount of water Required for Reconstitution
80 cc.	53 cc.
100 cc.	66 cc.
150 cc.	100 cc.
200 cc.	132 cc.

**SHAKE WELL BEFORE USING.**

Keep bottle tightly closed. The reconstituted suspension is stable for 7 days at room temperature (70° F) and 14 days under refrigeration (40° F).

**HOW SUPPLIED**

ALPEN ampicillin Capsules. Each capsule contains ampicillin trihydrate equivalent to 250 or 500 mg. ampicillin.

Product No. 3835 250 mg.

Product No. 3836 500 mg.

ALPEN for Oral Suspension. Each 5 cc. of reconstituted oral suspension contains ampicillin trihydrate equivalent to 125 mg. or 250 mg. ampicillin.

125 mg./5 cc. Product No. 3840; bottles of 80 cc., 100 cc., 150 cc. and 200 cc.

250 mg./5 cc. Product No. 3841; bottles of 80 cc., 100 cc., 150 cc. and 200 cc.

Distributed by



**LEDERLE LABORATORIES DIVISION**

American Cyanamid Company, Pearl River, N.Y. 10965

REV: 4/74

KEEP TIGHTLY CLOSED  
SHAKE WELL BEFORE USING

When stored at room temperature discard unused portion after 7 days;  
when stored under refrigeration discard unused portion after 14 days.  
Control No. Date Reconstituted

Lederle

NDC 0005-3840-43

# Alpen\*

## Ampicillin

for  
**Oral Suspension**

equivalent to 2.0 Grams Ampicillin

Cherry Flavored

When Reconstituted Each 5 cc contains Ampicillin Trihydrate equivalent to

**125 mg.** Ampicillin

CAUTION: Federal law prohibits dispensing without prescription.

**80 CC** (when reconstituted)

\*NADA 145-011

Directions for Mixing  
Prior to Dispensing:  
Loosen powder, add a total of 53 cc of water in two portions and shake well after each addition.  
EACH 5 cc CONTAINS:  
Ampicillin trihydrate equivalent to 125 mg. Ampicillin.

USUAL DOSAGE:  
Children:  
50-100 mg./kg./day in divided doses every 6-8 hours.

Adults:  
250-500 mg. every 6 hours.

IMPORTANT:  
Read accompanying literature for indications, dosage and precautions.

Distributed by  
LEDERLE LABORATORIES  
DIVISION

American Cyanamid Company  
Pearl River, N.Y. 10965

Exp. Date

D3

KEEP TIGHTLY CLOSED  
SHAKE WELL BEFORE USING

When stored at room temperature discard unused portion after 7 days;  
when stored under refrigeration discard unused portion after 14 days.  
Control No. Date Reconstituted

Lederle

NDC 0005-3840-46

# Alpen\*

## Ampicillin

for  
**Oral Suspension**

equivalent to 2.5 Grams Ampicillin

Cherry Flavored

When Reconstituted Each 5 cc contains Ampicillin Trihydrate equivalent to

**125 mg.** Ampicillin

CAUTION: Federal law prohibits dispensing without prescription.

**100 CC** (when reconstituted)

Directions for Mixing  
Prior to Dispensing:  
Loosen powder, add a total of 66 cc of water in two portions and shake well after each addition.  
EACH 5 cc CONTAINS:  
Ampicillin trihydrate equivalent to 125 mg. Ampicillin.

USUAL DOSAGE:  
Children:  
50-100 mg./kg./day in divided doses every 6-8 hours.

Adults:  
250-500 mg. every 6 hours.

IMPORTANT:  
Read accompanying literature for indications, dosage and precautions.

Distributed by  
LEDERLE LABORATORIES  
DIVISION

American Cyanamid Company  
Pearl River, N.Y. 10965

Exp. Date

D3

**KEEP TIGHTLY CLOSED  
SHAKE WELL BEFORE USING**  
When stored at room temperature discard unused portion after 7 days;  
when stored under refrigeration discard unused portion after 14 days.  
Control No. Date Reconstituted



NDC 0005-  
3840-49

# Alpen\*

## Ampicillin

for  
**Oral Suspension**

equivalent to 3.75 Grams Ampicillin

**Cherry Flavored**

When Reconstituted Each 5 cc  
contains Ampicillin Trihydrate  
equivalent to

**125 mg.** Ampicillin

CAUTION: Federal law prohibits  
dispensing without prescription.

**150 cc** (when reconstituted)

Exp. Date

\*©872,458 of Mfr.

D3

**Directions for Mixing**  
**Prior to Dispensing:**  
Loosen powder, add a  
total of 100 cc of water  
in two portions and shake  
well after each addition.  
EACH 5 cc CONTAINS:  
Ampicillin trihydrate  
equivalent to 125 mg.  
Ampicillin.

**USUAL DOSAGE:**  
Children:  
50-100 mg./kg./day,  
in divided doses  
every 6-8 hours.

Adults:  
250-500 mg. every 6 hours.

**IMPORTANT:**  
Read accompanying  
literature for  
indications, dosage  
and precautions.

Distributed by  
**LEDERLE LABORATORIES  
DIVISION**  
American Cyanamid Company  
Pearl River, N.Y. 10965

**KEEP TIGHTLY CLOSED  
SHAKE WELL BEFORE USING**  
When stored at room temperature discard unused portion after 7 days;  
when stored under refrigeration discard unused portion after 14 days.  
Control No. Date Reconstituted



NDC 0005-  
3840-60

# Alpen\*

## Ampicillin

for  
**Oral Suspension**

equivalent to 5.0 Grams Ampicillin

**Cherry Flavored**

When Reconstituted Each 5 cc  
contains Ampicillin Trihydrate  
equivalent to

**125 mg.** Ampicillin

CAUTION: Federal law prohibits  
dispensing without prescription.

**200 cc** (when reconstituted)

Exp. Date

\*©872,458 of Mfr.

D3

**Directions for Mixing**  
**Prior to Dispensing:**  
Loosen powder, add a  
total of 132 cc of water  
in two portions and shake  
well after each addition.  
EACH 5 cc CONTAINS:  
Ampicillin trihydrate  
equivalent to 125 mg  
Ampicillin.

**USUAL DOSAGE:**  
Children:  
50-100 mg./kg./day  
in divided doses  
every 6-8 hours.

Adults:  
250-500 mg. every 6 hours.

**IMPORTANT:**  
Read accompanying  
literature for  
indications, dosage  
and precautions.

Distributed by  
**LEDERLE LABORATORIES  
DIVISION**  
American Cyanamid Company  
Pearl River, N.Y. 10965

KEEP TIGHTLY CLOSED  
SHAKE WELL BEFORE USING

When stored at room temperature discard unused portion after 7 days;  
when stored under refrigeration discard unused portion after 14 days.  
Control No. \_\_\_\_\_ Date Reconstituted \_\_\_\_\_

Exp. Date \_\_\_\_\_

**Lederle** NDC 0005-3841-43

# Alpen\*

## Ampicillin

for  
**Oral Suspension**

equivalent to 4.0 Grams Ampicillin

**Cherry Flavored**

When Reconstituted Each 5 cc contains Ampicillin Trihydrate equivalent to

**250 mg.** Ampicillin

CAUTION: Federal law prohibits dispensing without prescription.

**80 cc** (when reconstituted)

\*0.072, 458 of Mfr.

D3

Directions for Mixing  
Prior to Dispensing:  
Loosen powder, add a total of 53 cc of water in two portions and shake well after each addition.

EACH 5 cc CONTAINS:  
Ampicillin trihydrate equivalent to 250 mg. Ampicillin.

USUAL DOSAGE:  
Children:  
50-100 mg./kg./day in divided doses every 6-8 hours.

Adults:  
250-500 mg. every 6 hours.

IMPORTANT:  
Read accompanying literature for indications, dosage and precautions.

Distributed by  
LEDERLE LABORATORIES  
DIVISION  
American Cyanamid Company  
Pearl River, N.Y. 10965

KEEP TIGHTLY CLOSED  
SHAKE WELL BEFORE USING

When stored at room temperature discard unused portion after 7 days;  
when stored under refrigeration discard unused portion after 14 days.  
Control No. \_\_\_\_\_ Date Reconstituted \_\_\_\_\_

Exp. Date \_\_\_\_\_

**Lederle** NDC 0005-3841-43

# Alpen\*

## Ampicillin

for  
**Oral Suspension**

equivalent to 5.0 Grams Ampicillin

**Cherry Flavored**

When Reconstituted Each 5 cc contains Ampicillin Trihydrate equivalent to

**250 mg.** Ampicillin

CAUTION: Federal law prohibits dispensing without prescription.

**100 cc** (when reconstituted)

Directions for Mixing  
Prior to Dispensing:  
Loosen powder, add a total of 66 cc of water in two portions and shake well after each addition.

EACH 5 cc CONTAINS:  
Ampicillin trihydrate equivalent to 250 mg. Ampicillin.

USUAL DOSAGE:  
Children:  
50-100 mg./kg./day in divided doses every 6-8 hours.

Adults:  
250-500 mg. every 6 hours.

IMPORTANT:  
Read accompanying literature for indications, dosage and precautions.

Distributed by  
LEDERLE LABORATORIES  
DIVISION  
American Cyanamid Company  
Pearl River, N.Y. 10965

KEEP TIGHTLY CLOSED  
SHAKE WELL BEFORE USING  
When stored at room temperature discard unused portion after 7 days;  
when stored under refrigeration discard unused portion after 14 days.  
Control No. Date Reconstituted



NDC 0005-3841-49

# Alpen\*

## Ampicillin

for  
**Oral Suspension**

equivalent to 7.5 Grams Ampicillin

### Cherry Flavored

When Reconstituted Each 5 cc contains Ampicillin Trihydrate equivalent to

**250 mg.** Ampicillin

CAUTION: Federal law prohibits dispensing without prescription.

**150 cc** (when reconstituted)

Exp. Date

\* 872,458 of Wh.

D3

Directions for Mixing  
Prior to Dispensing:  
Loosen powder, add a total of 100 cc of water in two portions and shake well after each addition.  
EACH 5 cc CONTAINS: Ampicillin trihydrate equivalent to 250 mg. Ampicillin.  
USUAL DOSAGE:  
Children:  
50-100 mg./kg./day in divided doses every 6-8 hours.  
Adults:  
250-500 mg. every 6 hours.  
**IMPORTANT:**  
Read accompanying literature for indications, dosage and precautions.  
Distributed by  
LEDERLE LABORATORIES  
DIVISION  
American Cyanamid Company  
Pearl River, N.Y. 10965

KEEP TIGHTLY CLOSED  
SHAKE WELL BEFORE USING  
When stored at room temperature discard unused portion after 7 days;  
when stored under refrigeration discard unused portion after 14 days.  
Control No. Date Reconstituted



NDC 0005-3841-60

# Alpen\*

## Ampicillin

for  
**Oral Suspension**

equivalent to 10.0 Grams Ampicillin

### Cherry Flavored

When Reconstituted Each 5 cc contains Ampicillin Trihydrate equivalent to

**250 mg.** Ampicillin

CAUTION: Federal law prohibits dispensing without prescription.

**200 cc** (when reconstituted)

Exp. Date

\* 872,458 of Wh.

D2

Directions for Mixing  
Prior to Dispensing:  
Loosen powder, add a total of 132 cc of water in two portions and shake well after each addition.  
EACH 5 cc CONTAINS: Ampicillin trihydrate equivalent to 250 mg. Ampicillin.  
USUAL DOSAGE:  
Children:  
50-100 mg./kg./day in divided doses every 6-8 hours.  
Adults:  
250-500 mg. every 6 hours.  
**IMPORTANT:**  
Read accompanying literature for indications, dosage and precautions.  
Distributed by  
LEDERLE LABORATORIES  
DIVISION  
American Cyanamid Company  
Pearl River, N.Y. 10965

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**Approval Package for:**

**APPLICATION NUMBER:**

**60-666 supplement**

Trade Name: Totacillin for Oral Suspension  
125mg/5mL and 250mg/5mL

Generic Name: ampicillin trihydrate

Sponsor: Beecham-Massengill Pharmaceuticals

Approval Date: July 23, 1974

# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:**

**60-666 supplement**

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**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**APPROVAL LETTER**

*Beecham-Massengill Pharmaceuticals*

DIVISION OF BEECHAM INC. CLIFTON, NEW JERSEY

*JFH*

**BMP**

65 INDUSTRIAL SOUTH  
CLIFTON, NEW JERSEY 07012  
REGULATORY DEPARTMENT

CABLE ADDRESS "BEECHPROD"  
TELEX 133471

PHONE: 201-778-9000

July 12, 1974

Date Approved 7/23/74

Account No. \_\_\_\_\_

Food and Drug Administration  
Div. of Anti-Infective Drug Products  
Certifiable Drug Review Staff (HFD-145)  
Bureau of Drugs  
5600 Fishers Lane  
Rockville, Maryland 20852

Signed *J. D. Harrison*  
for the U.S. Department of Food and Drugs  
Department of Health, Education and  
Welfare

Re: #60-666 (440.107c)

Gentlemen:

Reference is made to Beecham-Massengill Pharmaceuticals' approved Form 6 Antibiotic Application for Ampicillin Trihydrate for Oral Suspension.

We hereby wish to supplement our Application to provide for final printed labeling which reflects the labeling changes required by the revised Ampicillin Regulations.

This supplement is submitted in triplicate.

Sincerely,

BEECHAM-MASSENGILL PHARMACEUTICALS

*G. Vadnai*

George Vadnai  
Manager, Governmental Affairs



**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**FINAL PRINTED LABELING**

**KEEP TIGHTLY CLOSED** • **SHAKE WELL BEFORE USING**  
Any unused portion of the reconstituted suspension must be discarded after 7 days at room temperature (70°F) or 14 days under refrigeration (40°F).

Control No.

Exp. Date

Tear along perforation

**IMPORTANT:** Read accompanying package insert for details on dosage, indications and precautions.

**CAUTION:** Federal law prohibits dispensing without prescription.

NDC 0029-6625-23  
**BMP**  
**TOTACILLIN®**  
Ampicillin  
for Oral Suspension

Equivalent to  
2.5 Gm. Ampicillin

When reconstituted  
each 5 cc. will contain

**125 mg.**

Ampicillin as the trihydrate

**100 cc. (3 1/3 fl. oz.)**

*Beecham-Massengill*  
PHARMACEUTICALS  
DIV. OF BEECHAM INC. BRISTOL, TENN. 37620

TOTACILLIN® is a Registered Trademark

**DIRECTIONS FOR MIXING:**

Add 100 cc. of water to the bottle. For ease of preparation, add water in two portions. Shake well after each addition of water. Each 5 cc. (1 teaspoonful) will then contain ampicillin trihydrate equivalent to 125 mg. ampicillin.

**USUAL DOSAGE:**

Children: 250-500 mg. every 6-8 hours.  
Adults: 250-500 mg. every 6 hours.

Made in U.S.A. 6446/A

**KEEP TIGHTLY CLOSED** • **SHAKE WELL BEFORE USING**  
Any unused portion of the reconstituted suspension must be discarded after 7 days at room temperature (70°F) or 14 days under refrigeration (40°F).

Control No.

Exp. Date

Tear along perforation

**IMPORTANT:** Read accompanying package insert for details on dosage, indications and precautions.

**CAUTION:** Federal law prohibits dispensing without prescription.

NDC 0029-6625-21  
**BMP**  
**TOTACILLIN®**  
Ampicillin  
for Oral Suspension

Equivalent to  
2.0 Gm. Ampicillin

When reconstituted  
each 5 cc. will contain

**125 mg.**

Ampicillin as the trihydrate

**80 cc. (2 2/3 fl. oz.)**

*Beecham-Massengill*  
PHARMACEUTICALS  
DIV. OF BEECHAM INC. BRISTOL, TENN. 37620

TOTACILLIN® is a Registered Trademark

**DIRECTIONS FOR MIXING:**

Add 80 cc. of water to the bottle. For ease of preparation, add water in two portions. Shake well after each addition of water. Each 5 cc. (1 teaspoonful) will then contain ampicillin trihydrate equivalent to 125 mg. ampicillin.

**USUAL DOSAGE:**

Children: 50-100 mg./kg./day in divided doses every 6-8 hours.  
Adults: 250-500 mg. every 6 hours.

Made in U.S.A. 6306/A

**KEEP TIGHTLY CLOSED • SHAKE WELL BEFORE USING**  
Any unused portion of the reconstituted suspension must be discarded after 7 days at room temperature (70°F) or 14 days under refrigeration (40°F).

Control No.

Tear along perforation

Exp. Date

**IMPORTANT:** Read accompanying package insert for details on dosage, indications and precautions.

**CAUTION:** Federal law prohibits dispensing without prescription.

NDC 0029-6625-22  
**BMP**  
**TOTACILLIN®**  
Ampicillin  
for Oral Suspension

Equivalent to  
3.75 Gm. Ampicillin  
When reconstituted  
each 5 cc. will contain

**125 mg.**

Ampicillin as the trihydrate  
**150 cc. (5 fl. oz.)**

**Beecham-Massengill**  
PHARMACEUTICALS  
DIV. OF BEECHAM INC. BRISTOL, TENN. 37620

TOTACILLIN® is a Registered Trademark

**DIRECTIONS FOR MIXING:**  
Add a total of 100 cc. of water to the bottle. For ease of preparation, add water in two portions. Shake well after each addition of water. Each 5 cc. (1 teaspoonful) will then contain ampicillin trihydrate equivalent to 125 mg. ampicillin.

**USUAL DOSAGE:**  
Children: 50-100 mg./kg./day in divided doses every 6-8 hours.  
Adults: 250-500 mg. every 6 hours.

Made in U.S.A. 6309/B

**KEEP TIGHTLY CLOSED • SHAKE WELL BEFORE USING**  
Any unused portion of the reconstituted suspension must be discarded after 7 days at room temperature (70°F) or 14 days under refrigeration (40°F).

Control No.

Tear along perforation

Exp. Date

**IMPORTANT:** Read accompanying package insert for details on dosage, indications and precautions.

**CAUTION:** Federal law prohibits dispensing without prescription.

NDC 0029-6625-24  
**BMP**  
**TOTACILLIN®**  
Ampicillin  
for Oral Suspension

Equivalent to  
5.0 Gm. Ampicillin

When reconstituted  
each 5 cc. will contain

**125 mg.**

Ampicillin as the trihydrate

**200 cc. (6¾ fl. oz.)**

**Beecham-Massengill**  
PHARMACEUTICALS  
DIV. OF BEECHAM INC. BRISTOL, TENN. 37620

TOTACILLIN® is a Registered Trademark

**DIRECTIONS FOR MIXING:**  
Add a total of 132 cc. of water to the bottle. For ease of preparation, add water in two portions. Shake well after each addition of water. Each 5 cc. (1 teaspoonful) will then contain ampicillin trihydrate equivalent to 125 mg. ampicillin.

**USUAL DOSAGE:**  
Children: 50-100 mg./kg./day in divided doses every 6-8 hours.  
Adults: 250-500 mg. every 6 hours.

Made in U.S.A. 6447/A

**KEEP TIGHTLY CLOSED** • **SHAKE WELL BEFORE USING**  
Any unused portion of the reconstituted suspension must be discarded after 7 days at room temperature (70°F) or 14 days under refrigeration (40°F).

Control No.

Exp. Date

Tear along perforation

**IMPORTANT:** Read accompanying package insert for details on dosage, indications and precautions.

**CAUTION:** Federal law prohibits dispensing without prescription.

NDC 0029-6630-21  
**BMP**  
**TOTACILLIN®**  
Ampicillin  
for Oral Suspension

Equivalent to  
4.0 Gm. Ampicillin

When reconstituted  
each 5 cc. will contain

**250 mg.**

Ampicillin as the trihydrate

**80 cc. (2 $\frac{2}{3}$  fl. oz.)**

**Beecham-Massengill**  
PHARMACEUTICALS  
DIV. OF BEECHAM INC. BRISTOL, TENN. 37620

TOTACILLIN® is a Registered Trademark

**DIRECTIONS FOR MIXING:** Add 4.0 Gm. of water to the bottle. For ease of preparation, add water in two portions. Shake well after each addition of water. Each 5 cc. (1 teaspoonful) will then contain ampicillin trihydrate equivalent to 250 mg. ampicillin.

**USUAL DOSAGE:**  
Children: 50-100 mg./kg./day, in divided doses every 6-8 hours.  
Adults: 250-500 mg. every 6 hours.

Made in U.S.A. 6312/A

**KEEP TIGHTLY CLOSED** • **SHAKE WELL BEFORE USING**  
Any unused portion of the reconstituted suspension must be discarded after 7 days at room temperature (70°F) or 14 days under refrigeration (40°F).

Control No.

Exp. Date

Tear along perforation

**IMPORTANT:** Read accompanying package insert for details on dosage, indications and precautions.

**CAUTION:** Federal law prohibits dispensing without prescription.

NDC 0029-6630-23  
**BMP**  
**TOTACILLIN®**  
Ampicillin  
for Oral Suspension

Equivalent to  
5.0 Gm. Ampicillin

When reconstituted  
each 5 cc. will contain

**250 mg.**

Ampicillin as the trihydrate

**100 cc. (3 $\frac{1}{2}$  fl. oz.)**

**Beecham-Massengill**  
PHARMACEUTICALS  
DIV. OF BEECHAM INC. BRISTOL, TENN. 37620

TOTACILLIN® is a Registered Trademark

**DIRECTIONS FOR MIXING:** Add a total of 5.0 cc. of water to the bottle. For ease of preparation, add water in two portions. Shake well after each addition of water. Each 5 cc. (1 teaspoonful) will then contain ampicillin trihydrate equivalent to 250 mg. ampicillin.

**USUAL DOSAGE:**  
Children: 50-100 mg./kg./day, in divided doses every 6-8 hours.  
Adults: 250-500 mg. every 6 hours.

Made in U.S.A. 6448/A

**KEEP TIGHTLY CLOSED** • **SHAKE WELL BEFORE USING**  
Any unused portion of the reconstituted suspension must be discarded after 7 days at room temperature (70°F) or 14 days under refrigeration (40°F).

Control No. \_\_\_\_\_

Exp. Date \_\_\_\_\_

Tear along perforation

**IMPORTANT:** Read accompanying package insert for details on dosage, indications and precautions.

**CAUTION:** Federal law prohibits dispensing without prescription.

NDC 0029-6630-24  
**BMP**  
**TOTACILLIN®**  
Ampicillin  
for Oral Suspension

Equivalent to  
10.0 Gm. Ampicillin

When reconstituted  
each 5 cc. will contain

**250 mg.**

Ampicillin as the trihydrate

**200 cc. (6 7/8 fl. oz.)**

**Beecham-Massengill**  
PHARMACEUTICALS  
DIV. OF BEECHAM INC. BRISTOL, TENN. 37620

TOTACILLIN® is a Registered Trademark

**DIRECTIONS FOR MIXING:**  
Add a total of 1132 cc. of water to the bottle. For ease of preparation, add water in two portions. Shake well after each addition of water. Each 5 cc. (1 teaspoonful) will then contain ampicillin trihydrate equivalent to 250 mg. ampicillin.

**USUAL DOSAGE:**  
Children: 50-100 mg./kg./day in divided doses every 6-8 hours.  
Adults: 250-500 mg. every 6 hours.

Made in U.S.A. 6449/A

**KEEP TIGHTLY CLOSED** • **SHAKE WELL BEFORE USING**  
Any unused portion of the reconstituted suspension must be discarded after 7 days at room temperature (70°F) or 14 days under refrigeration (40°F).

Control No. \_\_\_\_\_

Exp. Date \_\_\_\_\_

Tear along perforation

**IMPORTANT:** Read accompanying package insert for details on dosage, indications and precautions.

**CAUTION:** Federal law prohibits dispensing without prescription.

NDC 0029-6630-22  
**BMP**  
**TOTACILLIN®**  
Ampicillin  
for Oral Suspension

Equivalent to  
7.50 Gm. Ampicillin

When reconstituted  
each 5 cc. will contain

**250 mg.**

Ampicillin as the trihydrate

**150 cc. (5 fl. oz.)**

**Beecham-Massengill**  
PHARMACEUTICALS  
DIV. OF BEECHAM INC. BRISTOL, TENN. 37620

TOTACILLIN® is a Registered Trademark

**DIRECTIONS FOR MIXING:**  
Add a total of 100 cc. of water to the bottle. For ease of preparation, add water in two portions. Shake well after each addition of water. Each 5 cc. (1 teaspoonful) will then contain ampicillin trihydrate equivalent to 250 mg. ampicillin.

**USUAL DOSAGE:**  
Children: 50-100 mg./kg./day in divided doses every 6-8 hours.  
Adults: 250-500 mg. every 6 hours.

Made in U.S.A. 6315/B

# Beecham-Massengill

## TOTACILLIN® AMPICILLIN

CAPSULES  
250 mg.  
and  
500 mg.

for  
ORAL SUSPENSION  
125 mg./5 cc.  
and  
250 mg./5 cc.

### DESCRIPTION

TOTACILLIN (ampicillin) is derived from the penicillin nucleus, 6-amino-penicillanic acid (6-APA), isolated by Beecham. Chemically it is D (-)- $\alpha$ -aminobenzyl penicillin trihydrate.

### ACTIONS

#### MICROBIOLOGY:

TOTACILLIN (ampicillin) is similar to benzyl penicillin in its bactericidal action against sensitive organisms during the stage of active multiplication. It acts through the inhibition of biosynthesis of cell wall mucopeptide. TOTACILLIN (ampicillin) differs in *in vitro* spectrum from benzyl penicillin in the Gram-negative spectrum. It exerts high *in vitro* activity against many strains of *Haemophilus influenzae*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Neisseria catarrhalis*, *Escherichia coli*, *Proteus mirabilis*, *Bacteroides funduliformis*, *Salmonellae* and *Shigellae*.

*In vitro* studies have also demonstrated the sensitivity of many strains of the following Gram-positive bacteria: alpha- and beta-hemolytic streptococci, *Diplococcus pneumoniae*, nonpenicillinase-producing staphylococci, *Bacillus anthracis*, and most strains of enterococci and clostridia. Ampicillin generally provides less *in vitro* activity than penicillin G against Gram-positive bacteria. Because it does not resist destruction by penicillinase, it is not effective against penicillinase-producing bacteria, particularly resistant staphylococci. All strains of *Pseudomonas* and most strains of *Klebsiella* and *Aerobacter* are resistant.

#### PHARMACOLOGY:

TOTACILLIN (ampicillin) is acid stable and, therefore, well absorbed. Food, however, retards absorption. Blood serum levels of approximately 2 mcg./ml. are attained within 1-2 hours following a 250 mg. oral dose given to fasting adults. Detectable amounts persist for about 6 hours. TOTACILLIN (ampicillin) diffuses readily into all body tissues and fluids with the exception of brain and spinal fluid except when meninges are inflamed. Higher serum levels are obtained following I.M. injection. Most of the ampicillin is excreted unchanged in the urine and this excretion can be delayed by concurrent administration of probenecid. The active form appears in the bile in higher concentrations than found in the serum. TOTACILLIN (ampicillin) is one of the least serum bound of all the penicillins, averaging about 20% compared to approximately 60%-90% for other penicillins.

### INDICATIONS

TOTACILLIN (ampicillin) is indicated in the treatment of infections due to susceptible strains of the following:

Gram-negative Organisms: *Shigellae*, *Salmonellae* (including *S. typhosa*), *H. influenzae*, *E. coli*, *P. mirabilis*, *N. gonorrhoeae*, and *N. meningitidis*.

Gram-positive Organisms: Streptococci, *D. pneumoniae*, and non-penicillinase-producing staphylococci.

Because of its wide spectrum and bactericidal action, it may be useful in instituting therapy; however, bacteriological studies to determine the causative organisms and their sensitivity to ampicillin should be performed.

Indicated surgical procedures should be performed.

### CONTRAINDICATIONS

The use of this drug is contraindicated in individuals with a history of an allergic reaction to any of the penicillins.

### WARNINGS

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL THERAPY, IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. THESE REACTIONS ARE MORE APT TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR HYPERSENSITIVITY REACTIONS TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE THERAPY WITH A PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, THE DRUG SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE, OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

#### USAGE IN PREGNANCY:

Safety for use in pregnancy has not been established.

### PRECAUTIONS

As with any antibiotic preparation, constant observation for signs of overgrowth of nonsusceptible organisms, including fungi, is essential. Should superinfection occur (usually involving *Aerobacter*, *Pseudomonas*, or *Candida*), the drug should be discontinued and /or appropriate therapy instituted. As with any potent agent, it is advisable to check periodically for organ system dysfunction during prolonged therapy; this includes renal, hepatic, and hematopoietic systems. This is particularly important in prematures, neonates and other infants.

### ADVERSE REACTIONS

As with other penicillins, it may be expected that untoward reactions will be essentially limited to sensitivity phenomena. They are more likely to occur in individuals who have previously demonstrated hypersensitivity to penicillins and in those with a history of allergy, asthma, hay fever, or

(Continued on other side)



**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**Approval Package for:**

**APPLICATION NUMBER:**

**60-666 supplement**

Trade Name: Pen A for Oral Suspension  
125mg/5mL and 250mg/5mL

Generic Name: ampicillin trihydrate

Sponsor: Beecham-Massengill Pharmaceuticals

Approval Date: September 3, 1974

# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:**

**60-666 supplement**

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Approval Letter(s)	X
Tentative Approval Letter(s)	
Final Printed Labeling	X
CSO Labeling Review(s)	
Medical Officer Review(s)	
Chemistry Review(s)	
Microbiology Review(s)	
Bioequivalence Review(s)	
Administrative Document(s)	
Correspondence	

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**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**APPROVAL LETTER**

1

AG  
Power

# Beecham-Massengill Pharmaceuticals

DIVISION OF BEECHAM INC. CLIFTON, NEW JERSEY

**BMP**

65 INDUSTRIAL SOUTH  
CLIFTON, NEW JERSEY 07012  
REGULATORY DEPARTMENT

CABLE ADDRESS "BEECHPROD"  
TELEX 133471  
PHONE: 201-778-9000

*OK to sign out  
JPT 9/3/74*

August 26, 1974

(For use of Food and Drug Administration)

Date approved 9/3/74

Account No. \_\_\_\_\_

Signed *George Vadnai*

For the Director of Food and Drugs  
Food and Drug Administration  
Department of Health, Education, and Welfare

Food and Drug Administration  
Div. of Anti-Infective Drug Products  
Certifiable Drug Review Staff (HFD-145)  
Bureau of Drugs  
5600 Fishers Lane  
Rockville, Maryland 20852

Re: #60-666 (440.107c)

Gentlemen:

Reference is made to Beecham-Massengill Pharmaceuticals' approved Form 6 #60-666 covering Ampicillin Trihydrate for Oral Suspension, distributed by Pfizer Inc. under the trade name Pen A.

We are submitting, in triplicate, final printed labeling which reflect the labeling changes required by the recently revised Ampicillin Regulations.

Sincerely,

BEECHAM-MASSENGILL PHARMACEUTICALS

*G. Vadnai*

George Vadnai  
Manager, Governmental Affairs

GSV:dmm

Enclosures

6608

SEP 3 1974

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**FINAL PRINTED LABELING**

**Pen A**<sup>®</sup>**ampicillin**

CAPSULES  
250 mg  
and  
500 mg

for  
ORAL SUSPENSION  
125 mg/5 ml  
and  
250 mg/5 ml

**Description**

Pen A (ampicillin) is derived from the penicillin nucleus, 6-amino-penicillanic acid (6-APA). Chemically it is D (-)  $\alpha$ -aminobenzyl penicillin.

**Actions****MICROBIOLOGY:**

Pen A (ampicillin) is similar to benzyl penicillin in its bactericidal action against sensitive organisms during the stage of active multiplication. It acts through the inhibition of biosynthesis of cell wall mucopeptide. Pen A (ampicillin) differs in *in vitro* spectrum from benzyl penicillin in the gram-negative spectrum. It exerts high *in vitro* activity against many strains of *Hemophilus influenzae*, *Neisseria gonorrhoeae*, *Neisseria meningitidis* and *Neisseria catarrhalis*, *Escherichia coli*, *Proteus mirabilis*, *Bacteroides funduliformis*, *Salmonellae* and *Shigellae*.

*In vitro* studies have also demonstrated the sensitivity of many strains of the following gram-positive bacteria: alpha- and beta-hemolytic streptococci, *Diplococcus pneumoniae*, nonpenicillinase-producing staphylococci, *Bacillus anthracis*, and most strains of enterococci and clostridia. Ampicillin generally provides less *in vitro* activity than penicillin G against gram-positive bacteria. Because it does not resist destruction by penicillinase, it is not effective against penicillinase-producing bacteria, particularly resistant staphylococci. All strains of *Pseudomonas* and most strains of *Klebsiella* and *Aerobacter* are resistant.

**PHARMACOLOGY:**

Pen A (ampicillin) is acid stable and therefore well absorbed. Food, however, retards absorption. Blood serum levels of approximately 2 mcg/ml are attained within 1-2 hours following a 250 mg oral dose given to fasting adults. Detectable amounts persist for about 6 hours. Pen A (ampicillin) diffuses readily into all body tissues and fluids with the exception of brain and spinal fluid except when meninges are inflamed. Higher serum levels are obtained following I.M. injection. Most of the ampicillin is excreted unchanged in the urine and this excretion can be delayed by concurrent administration of probenecid. The active form appears in the bile in higher concentrations than found in the serum. Pen A (ampicillin) is the least serum bound of all the penicillins, averaging about 20% compared to approximately 60%-90% for other penicillins.

**Indications**

Pen A (ampicillin) is indicated in the treatment of infections due to susceptible strains of the following:

*gram-negative organisms*—*Shigellae*, *Salmonellae* (including *S. typhosa*), *H. influenzae*, *E. coli* and *P. mirabilis*, *N. gonorrhoeae*, and *N. meningitidis*;  
*gram-positive organisms*—Streptococci, *D. pneumoniae*, and nonpenicillinase-producing staphylococci.

Because of its wide spectrum and bactericidal action, it may be useful in instituting therapy; however, bacteriological studies to determine the causative organisms and their sensitivity to ampicillin should be performed.

Indicated surgical procedures should be performed.

**Contraindications**

The use of this drug is contraindicated in individuals with a history of an allergic reaction to any of the penicillins.

**Warnings**

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL THERAPY, IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. THESE REACTIONS ARE MORE APT TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR HYPERSENSITIVITY REACTIONS TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE THERAPY WITH A PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, THE DRUG SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED.

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE, OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

**USAGE IN PREGNANCY:**

Safety for use in pregnancy has not been established.

**Precautions**

As with any antibiotic preparation, constant observations for signs of overgrowth of nonsusceptible organisms, including fungi, are essential. Should superinfection occur (usually involving *Aerobacter*, *Pseudomonas*, or *Candida*), the drug should be discontinued and/or appropriate therapy instituted. As with

*Precautions (continued)*

any potent agent, it is advisable to check periodically for organ system dysfunction during prolonged therapy; this includes renal, hepatic, and hematopoietic systems. This is particularly important in prematures, neonates and other infants.

**Adverse Reactions**

As with other penicillins, it may be expected that untoward reactions will be essentially limited to sensitivity phenomena. They are more likely to occur in individuals who have previously demonstrated hypersensitivity to penicillins and in those with a history of allergy, asthma, hay fever, or urticaria. The following adverse reactions have been reported as associated with the use of ampicillin:

*Gastrointestinal*—glossitis, stomatitis, black "hairy" tongue, nausea, vomiting, and diarrhea. (These reactions are usually associated with oral dosage forms.)

*Hypersensitivity reactions*—An erythematous maculopapular rash has been reported fairly frequently. Urticaria and erythema multiforme have been reported occasionally. A few cases of exfoliative dermatitis have been reported. Anaphylaxis is the most serious reaction experienced and has usually been associated with the parenteral dosage form.

*Note:* Urticaria, other skin rashes, and serum sickness-like reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, ampicillin should be discontinued, unless, in the opinion of the physician, the condition being treated is life-threatening and amenable only to ampicillin therapy.

*Liver*—A moderate rise in serum glutamic oxaloacetic transaminase (SGOT) has been noted, particularly in infants, but the significance of this finding is unknown.

*Hemic and Lymphatic Systems*—Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia, and agranulocytosis have been reported during therapy with the penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be sensitivity reactions.

**Dosage**

*Infections of the ear, nose, throat, and lower respiratory tract* due to streptococci, pneumococci, and nonpenicillinase-producing staphylococci, and also those infections of the upper and lower respiratory tract due to *H. influenzae*:

- Adults— 250 mg every 6 hours.
- Children— 50 mg/kg/day in divided doses every 6 or 8 hours.

*Infections of the genitourinary tract caused by sensitive gram-negative and gram-positive bacteria:*

- Adults— 500 mg every 6 hours. Larger doses may be required for severe infections.
- Children— 100 mg/kg/day in divided doses every 6 hours.

*Uncomplicated urethritis due to N. gonorrhoeae:*

Adult males and females—3.5 grams single oral dose administered simultaneously with 1.0 gram of probenecid.

*Cases of gonorrhea with a suspected lesion of syphilis should have dark field examinations before receiving ampicillin, and monthly serological tests for a minimum of 4 months.*

*Infections of the gastrointestinal tract:*

- Adults— 500 mg every 6 hours.
- Children— 100 mg/kg/day in divided doses every 6 hours.

Larger doses may be required for stubborn or severe infections. The children's dosage is intended for individuals whose weight will not cause a dosage to be calculated greater than that recommended for adults. Children weighing more than 20 kg should be dosed according to the adult recommendations.

It should be recognized that in the treatment of chronic urinary tract and intestinal infections, frequent bacteriological and clinical appraisals are necessary. Smaller doses than those recommended above should not be used. Even higher doses may be needed at times. In stubborn infections, therapy may be required for several weeks. It may be necessary to continue clinical and/or bacteriological follow-up for several months after cessation of therapy.

Treatment should be continued for a minimum of 48 to 72 hours beyond the time that the patient becomes asymptomatic or evidence of bacterial eradication has been obtained. It is recommended that there be at least 10 days' treatment for any infection caused by hemolytic streptococci, to help prevent the occurrence of acute rheumatic fever or glomerulonephritis.

**Directions for Mixing Oral Suspension**

Prepare suspension at time of dispensing as follows: Add 66 ml of water to the 100 ml package and 132 ml of water to the 200 ml package. Shake vigorously. This will provide 100 and 200 ml of suspension, respectively. Each teaspoonful (5 ml) will contain 125 mg or 250 mg ampicillin. SHAKE WELL BEFORE USING. Keep bottle tightly closed. The reconstituted suspension is stable for 7 days at room temperature (70°F.) or 14 days under refrigeration (40°F.).

**How Supplied**

Pen A (ampicillin) Capsules: Ampicillin trihydrate equivalent to 250 mg or 500 mg ampicillin per capsule.

250 mg: bottles of 100, 500, and unit dose (10 x 10's).

500 mg: bottles of 100, and unit dose (10 x 10's).

Pen A (ampicillin) for Oral Suspension: Each 5 ml of reconstituted suspension contains ampicillin trihydrate equivalent to 125 mg or 250 mg ampicillin.

125 mg/5 ml: bottles of 100 ml and 200 ml.

250 mg/5 ml: bottles of 100 ml and 200 ml.

Distributed by  
**PFIZER LABORATORIES DIVISION**  
PFIZER INC.

60-2096-00-4  
9049/A

NEW YORK, N.Y. 10017

Printed in U.S.A.  
Revised May 1974

NDC 0069-0311-44 2394

# Pen A<sup>®</sup>

ampicillin  
FOR ORAL  
SUSPENSION  
125 mg/5 ml<sup>†</sup>  
100 ml

equivalent to  
2.5 g ampicillin

CAUTION: Federal law prohibits  
dispensing without prescription.



READ ACCOMPANYING  
PROFESSIONAL INFORMATION

USUAL DOSAGE  
Children: 50 to 100 mg/kg/day in divided doses  
every 6 to 8 hours.  
Adults: 250 to 500 mg every 6 hours.

9022/A

**RECOMMENDED STORAGE IN DRY FORM**  
STORE BELOW 86° F. (30° C.)  
When reconstituted as directed each 5 ml (1 teaspoonful) contains ampicillin trihydrate equivalent to 125 mg ampicillin.  
Directions for reconstitution: Add 86 ml of water. For ease of preparation, tap gently, add water in 2 portions. Shake well after each addition.  
EXP. MADE IN U.S.A. 1

LOT NO.

**KEEP CONTAINER TIGHTLY CLOSED - SHAKE WELL BEFORE USING**  
When suspension is stored at room temperature discard unused portion after 7 days; when stored under refrigeration discard unused portion after 14 days.

NDC 0069-0311-91 2395

# Pen A<sup>®</sup>

ampicillin  
FOR ORAL  
SUSPENSION  
125 mg/5 ml<sup>†</sup>  
200 ml

equivalent to  
5.0 g ampicillin

CAUTION: Federal law prohibits  
dispensing without prescription.



READ ACCOMPANYING  
PROFESSIONAL INFORMATION

USUAL DOSAGE  
Children: 50 to 100 mg/kg/day in divided doses  
every 6 to 8 hours.  
Adults: 250 to 500 mg every 6 hours.

9022/A

**RECOMMENDED STORAGE IN DRY FORM**  
STORE BELOW 86° F. (30° C.)  
When reconstituted as directed each 5 ml (1 teaspoonful) contains ampicillin trihydrate equivalent to 125 mg ampicillin.  
Directions for reconstitution: Add 132 ml of water. For ease of preparation, tap gently, add water in 2 portions. Shake well after each addition.  
EXP. MADE IN U.S.A. 1

LOT NO.

**KEEP CONTAINER TIGHTLY CLOSED - SHAKE WELL BEFORE USING**  
When suspension is stored at room temperature discard unused portion after 7 days; when stored under refrigeration discard unused portion after 14 days.

NDC 0069-0312-44 2396

# Pen A<sup>®</sup> ampicillin

FOR ORAL  
SUSPENSION

**250 mg/5 ml<sup>†</sup>**

**100 ml**

equivalent to  
5.0 g ampicillin

CAUTION: Federal law prohibits  
dispensing without prescription.

 Distributed by  
**LABORATORIES DIVISION**  
PFIZER INC., NEW YORK, N.Y. 10017

READ ACCOMPANYING  
PROFESSIONAL INFORMATION

USUAL DOSAGE

Children: 50 to 100 mg/kg/day in divided doses  
every 6 to 8 hours.  
Adults: 250 to 500 mg every 6 hours.

9019/V

**RECOMMENDED STORAGE IN DRY FORM**  
STORE BELOW 86° F. (30° C.)  
When reconstituted as directed each 5 ml (1 teaspoonful)  
contains ampicillin trihydrate equivalent to 250 mg ampicillin.  
Directions for reconstitution: Add 86 ml of water. For ease  
of preparation, tap gently, add water in 2 portions.  
Shake well after each addition.  
EXP.

MADE IN U.S.A. 1

LOT NO.

**KEEP CONTAINER TIGHTLY CLOSED—SHAKE WELL BEFORE USING**

When suspension is stored at room temperature discard  
unused portion after 7 days; when stored under  
refrigeration discard unused portion after 14 days.

NDC 0069-0312-91 2397

# Pen A<sup>®</sup> ampicillin

FOR ORAL  
SUSPENSION

**250 mg/5 ml<sup>†</sup>**

**200 ml**

equivalent to  
10.0 g ampicillin

CAUTION: Federal law prohibits  
dispensing without prescription.

 Distributed by  
**LABORATORIES DIVISION**  
PFIZER INC., NEW YORK, N.Y. 10017

READ ACCOMPANYING  
PROFESSIONAL INFORMATION

USUAL DOSAGE

Children: 50 to 100 mg/kg/day in divided doses  
every 6 to 8 hours.  
Adults: 250 to 500 mg every 6 hours.

9019/V

**RECOMMENDED STORAGE IN DRY FORM**  
STORE BELOW 86° F. (30° C.)  
When reconstituted as directed each 5 ml (1 teaspoonful)  
contains ampicillin trihydrate equivalent to 250 mg ampicillin.  
Directions for reconstitution: Add 132 ml of water. For ease  
of preparation, tap gently, add water in 2 portions.  
Shake well after each addition.  
EXP.

MADE IN U.S.A. 1

LOT NO.

**KEEP CONTAINER TIGHTLY CLOSED—SHAKE WELL BEFORE USING**

When suspension is stored at room temperature discard  
unused portion after 7 days; when stored under  
refrigeration discard unused portion after 14 days.

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**Approval Package for:**

**APPLICATION NUMBER:**

**60-666 supplement**

Trade Name: Penbritin for Oral Suspension  
125mg/5mL and 150mg/5mL

Generic Name: ampicillin trihydrate

Sponsor: Beecham-Massengill Pharmaceuticals

Approval Date: November 1, 1974

# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:**

**60-666 supplement**

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Microbiology Review(s)	
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Administrative Document(s)	
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**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**APPROVAL LETTER**

# Beecham-Massengill Pharmaceuticals

DIVISION OF BEECHAM INC. CLIFTON, NEW JERSEY

H 6  
Harrison

65 INDUSTRIAL SOUTH  
CLIFTON, NEW JERSEY 07012  
REGULATORY DEPARTMENT

**BMP**

CABLE ADDRESS "BEECHPROD"  
TELEX 133471

PHONE: 201-778-9000

October 28, 1974

Date Approved 11/1/74

Account No. \_\_\_\_\_

Food and Drug Administration  
Div. of Anti-Infective Drug Products  
Certifiable Drug Review Staff (HFD-145c)  
Bureau of Drugs  
5600 Fishers Lane  
Rockville, Maryland 20852

Signed John D. Harrison  
the Commissioner of Food and Drugs  
Department of Health, Education and  
Welfare

Re: #60-666 (440.107c)

Gentlemen:

Reference is made to Beecham-Massengill Pharmaceuticals' approved Form 6 Antibiotic Application #60-666 covering Ampicillin for Oral Suspension distributed by Ayerst Laboratories Inc. under the trade name Penbritin.

We are hereby submitting, in triplicate, a final printed package insert which is identical to the currently approved insert, except for a revision in the "How Supplied" section, to indicate the change from the anhydrous to the trihydrate formulation in the manufacture of Penbritin Pediatric Drops, approved by the Administration on October 8, 1974.

Sincerely,

BEECHAM-MASSENGILL PHARMACEUTICALS

*G. Vadnai*

George Vadnai  
Manager, Governmental Affairs

GSV:dmm

Enclosures

7573  
OCT 31 1974

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**FINAL PRINTED LABELING**

# PENBRITIN\*

(ampicillin)

for  
**ORAL SUSPENSION**  
125 mg./5 cc.  
and  
250 mg./5 cc.

**PEDIATRIC DROPS**  
for  
**ORAL SUSPENSION**  
100 mg./cc.

**CAUTION:** Federal law prohibits dispensing without prescription.

## DESCRIPTION

Chemical name: D(-)-alpha-aminobenzyl penicillin

PENBRITIN is an orally active, semisynthetic broad spectrum penicillin. It is inactivated by penicillinase.

## ACTIONS

### Microbiologic:

Ampicillin appears to act primarily by interfering with the synthesis or maintenance of the bacterial cell wall. It strongly inhibits the early lag and logarithmic phases of bacterial multiplication. In *in vitro* studies, ampicillin is bactericidal.

PENBRITIN is effective against the usual penicillin-susceptible gram-positive organisms, and in addition, many gram-negative pathogens. It is active *in vitro* against many strains of the following bacteria:

**GRAM-POSITIVE** — Alpha and beta hemolytic streptococci, nonpenicillinase-producing staphylococci, *Diplococcus pneumoniae*, *Clostridia* species, *Bacillus anthracis*, most strains of enterococci.

**GRAM-NEGATIVE** — *Haemophilus influenzae*, *Neisseria gonorrhoeae* and meningitidis, *Proteus mirabilis*, *Escherichia coli*, *Salmonella* (including *S. typhosa*), *Neisseria catarrhalis*, *Bacteroides funduliformis*, and *Shigella*.

All strains of *Pseudomonas* and most strains of *Klebsiella-Aerobacter* are resistant. Because ampicillin is destroyed by penicillinase, PENBRITIN is not effective against penicillinase-producing bacteria.

### Pharmacologic:

PENBRITIN is stable in acid and is therefore not destroyed by gastric juice. (Food, however, retards absorption.) PENBRITIN is well absorbed and produces high and persistent blood levels of unbound ampicillin. Ampicillin is the least protein bound of all the penicillins, averaging 20 percent as contrasted with 60 to 90 percent for the others. Blood serum levels of approximately 2 mcg./ml. are achieved within one to two hours following a 250 mg. oral dose to fasting adults. Detectable amounts persist in the blood for about six hours. There are high concentrations in the bile and urine. Ampicillin diffuses readily into most body tissues and fluids. However, penetration into the cerebral spinal fluid occurs only with meningeal inflammation. Ampicillin is excreted in the urine, largely unchanged, and this excretion can be delayed by concurrent administration of probenecid.

## INDICATIONS

PENBRITIN is indicated in the treatment of infections due to susceptible strains of the following:

**GRAM-NEGATIVE** organisms: *Shigella*, *Salmonella* (including *S. typhosa*), *H. influenzae*, *E. coli*, *P. mirabilis*, *N. gonorrhoeae*, and *N. meningitidis*.

**GRAM-POSITIVE** organisms: Streptococci, nonpenicillinase-producing staphylococci, and *D. pneumoniae*.

Bacteriologic studies to determine the causative organisms and their sensitivity to ampicillin should be performed. Because PENBRITIN is a broad spectrum antibiotic, therapy may be instituted prior to the results of sensitivity testing.

## CONTRAINDICATIONS

PENBRITIN is contraindicated in patients with a history of hypersensitivity to any penicillin.

## WARNINGS

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL THERAPY, IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. THESE REACTIONS ARE MORE APT TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR HYPERSENSITIVITY REACTIONS TO MULTIPLE ALLERGENS.

THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE THERAPY WITH A PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, AND OTHER ALLERGENS.

IF AN ALLERGIC REACTION OCCURS, THE DRUG SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE, OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

USAGE IN PREGNANCY: Safety for use in pregnancy has not been established.

## PRECAUTIONS

As with any antibiotic preparation, constant observation for signs of overgrowth of nonsusceptible organisms, including fungi, is essential. Should superinfection occur (usually involving *Aerobacter*, *Pseudomonas*, or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.

Periodic assessment of renal, hepatic, and hematopoietic function should be made during prolonged therapy. This is particularly important in prematures, neonates and other infants.

## ADVERSE REACTIONS

As with other penicillins, it may be expected that untoward reactions will be essentially limited to sensitivity phenomena. These are more likely to occur in individuals with a history of allergy, asthma, hay fever, or urticaria.

The following adverse reactions have been reported as associated with the use of ampicillin:

Gastrointestinal — glossitis, stomatitis, black "hairy" tongue, nausea, vomiting, diarrhea. (These reactions are usually associated with oral administration.)

# PENBRITIN (ampicillin) for Oral Suspension & Pediatric Drops for Oral Suspension cont'd.

Hypersensitivity reactions — erythematous maculopapular rashes have been reported fairly frequently; urticaria, erythema multiforme, and an occasional case of exfoliative dermatitis have been reported. Anaphylaxis is usually associated with parenteral administration.

*Note:* Urticaria, other skin rashes, and serum sickness-like reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, ampicillin should be discontinued unless, in the opinion of the physician, the condition being treated is life-threatening and amenable only to ampicillin therapy.

**Hepatic** — A moderate rise in serum glutamic oxaloacetic transaminase (SGOT) has been noted, particularly in infants. The significance of this finding is unknown.

**Hemic and lymphatic** — anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia, and agranulocytosis have been reported. These are usually reversible on discontinuation of the drug, and are believed to be hypersensitivity phenomena.

## DOSAGE AND ADMINISTRATION

Infection	Usual Dosage* Adults	Usual Dosage* Children†
Respiratory tract	250 mg. q. 6 h.	50 mg./kg./day in equal doses q. 6-8 h.
Gastrointestinal tract Genitourinary tract	500 mg. q. 6 h.	100 mg./kg./day in equal doses q. 6-8 h.
Urethritis in Males or Females due to <i>N. gonorrhoeae</i>	3.5 Gm. single oral dose administered simultaneously with 1.0 Gm. of probenecid  In the treatment of complications of gonorrheal urethritis, such as prostatitis and epididymitis, prolonged and intensive therapy is recommended.  Cases of gonorrhea with a suspected primary lesion of syphilis should have dark-field examinations before receiving treatment. In all other cases where concomitant syphilis is suspected, monthly serologic tests should be made for a minimum of four months.	

\* Larger than usual dosages may be required for stubborn or severe infections. Smaller doses than those recommended above should not be used.

† The children's dosage is intended for individuals whose weight will not cause a dosage to be calculated greater than that recommended for adults. Children weighing more than 20 kg. (44 lb.) should be given the adult recommended dosage.

## PEDIATRIC DROPS:

A suggested dosage regimen is:  
Under 12 lb. — 0.6 cc. q. 6 hours†  
12-25 lb. — 1.0 cc. q. 6 hours.  
25-44 lb. — 2.0 cc. q. 6 hours.

**DURATION OF TREATMENT:** Medications should be continued for at least 48 to 72 hours after all symptoms have subsided or cultures have become negative. For any infection caused by hemolytic streptococci, at least 10 days of treatment is recommended to help prevent the occurrence of acute rheumatic fever or glomerulonephritis.

## DIRECTIONS FOR MIXING ORAL SUSPENSIONS

Prepare suspensions at time of dispensing as follows: Add the required amount of water (see table below) to the bottle and shake vigorously. Each teaspoonful (5 cc.) of reconstituted Oral Suspension will contain 125 mg. or 250 mg. ampicillin, depending upon the initial concentration. Each cc. of reconstituted Pediatric Drops will contain 100 mg. ampicillin.

Bottle Size	Amount of Water Required for Reconstitution
100 cc. Oral Suspension	66 cc.
200 cc. Oral Suspension	132 cc.
20 cc. Pediatric Drops	11.5 cc.

SHAKE WELL BEFORE USING.

## STABILITY

**ORAL SUSPENSION:** No refrigeration required before mixing. After mixing, suspension may be kept at room temperature (70°F.) for 7 days or in a refrigerator (40°F.) for 14 days without significant loss of potency. KEEP TIGHTLY CLOSED.

**PEDIATRIC DROPS:** No refrigeration required before mixing. After mixing, suspension may be kept in a refrigerator for 14 days without significant loss of potency. KEEP TIGHTLY CLOSED.

## HOW SUPPLIED

**PENBRITIN (ampicillin) for Oral Suspension** — when reconstituted:

Each 5 cc. (one teaspoonful) contains 125 mg. ampicillin as the trihydrate. Bottles for 100 cc. (NDC 0046-0607-86) and 200 cc. (NDC 0046-0607-82).

Each individual-dose sealed envelope provides a single dose of ampicillin anhydrous equivalent to 125 mg. ampicillin. Packages of 40 (NDC 0046-0607-40).

Each 5 cc. (one teaspoonful) contains 250 mg. ampicillin as the trihydrate. Bottles for 100 cc. (NDC 0046-0611-86) and 200 cc. (NDC 0046-0611-82).

Each individual-dose sealed envelope provides a single dose of ampicillin anhydrous equivalent to 250 mg. ampicillin. Packages of 40 (NDC 0046-0611-40).

**PENBRITIN (ampicillin) PEDIATRIC DROPS for Oral Suspension** — when reconstituted:

Each cc. contains 100 mg. ampicillin as the trihydrate. Bottles for 20 cc. (NDC 0046-0625-20).

Distributed by  
**AYERST LABORATORIES INCORPORATED**  
New York, N.Y. 10017

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**Approval Package for:**

**APPLICATION NUMBER:**

**60-666 supplement**

Trade Name: Alpen for Oral Suspension  
125mg/5mL and 250mg/5mL

Generic Name: ampicillin trihydrate

Sponsor: Beecham-Massengill Pharmaceuticals

Approval Date: December 6, 1974

# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:**

**60-666 supplement**

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**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**APPROVAL LETTER**

H-6  
Powers

①

# Beecham-Massengill Pharmaceuticals

DIVISION OF BEECHAM INC. CLIFTON, NEW JERSEY

65 INDUSTRIAL SOUTH  
CLIFTON, NEW JERSEY 07012  
REGULATORY DEPARTMENT

CABLE ADDRESS "BEECHPROD"  
TELEX 133471

PHONE: 201-778-9000

**BMP**

*OK to sign out  
JEP 12/6/74*

December 3, 1974

Food and Drug Administration  
Div. of Anti-Infective Drug Products  
Certifiable Drug Review Staff (HFD-143)  
Bureau of Drugs  
5600 Fishers Lane  
Rockville, Maryland 20852

(For use of Food and Drug Administration)	
Date approved	12/6/74
Account No.	
Signed	<i>[Signature]</i>
For the Commissioner of Food and Drugs Food and Drug Administration Department of Health, Education, and Welfare	

Re: #60-666 (440.107c)

Gentlemen:

Reference is made to Beecham-Massengill Pharmaceuticals' approved Form 6 #60-666, covering Ampicillin for Oral Suspension, distributed by Lederle Laboratories under the trade name, Alpen.

We are submitting, in triplicate, a final printed insert, which reflects the addition of the manufacturer's identification.

Sincerely,

BEECHAM-MASSENGILL PHARMACEUTICALS

*J. Benta / G. Vadnai*

George Vadnai  
Manager, Governmental Affairs

8073



GSV:dmm

Enclosures



**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**FINAL PRINTED LABELING**

64359  
D8

# ALPEN\*

## AMPICILLIN

### for Oral Use

#### DESCRIPTION

ALPEN *ampicillin* is derived from the penicillin nucleus, 6-aminopenicillanic acid (6-APA). Chemically it is D (-)  $\alpha$ -aminobenzylpenicillin trihydrate.

#### ACTIONS

##### MICROBIOLOGY:

Ampicillin is similar to benzyl penicillin in its bactericidal action against sensitive organisms during the stage of active multiplication. It acts through the inhibition of biosynthesis of cell wall mucopeptide. Ampicillin differs in *in vitro* spectrum from benzylpenicillin in the Gram-negative spectrum. It exerts high *in vitro* activity against many strains of *Hemophilus influenzae*, *Neisseria gonorrhoeae*, *Neisseria meningitidis* and *Neisseria catarrhalis*, *Escherichia coli*, *Proteus mirabilis*, *Bacteroides funduliformis*, *Salmonellae*, and *Shigellae*.

*In vitro* studies have also demonstrated the sensitivity of many strains of the following Gram-positive bacteria: alpha- and beta-hemolytic streptococci, *Diplococcus pneumoniae*, nonpenicillinase-producing staphylococci, *Bacillus anthracis*, and most strains of enterococci and clostridia. Ampicillin generally provides less *in vitro* activity than penicillin-G against Gram-positive bacteria. Because it does not resist destruction by penicillinase it is *not* effective against penicillinase-producing bacteria, particularly resistant staphylococci. All strains of *Pseudomonas* and most strains of *Klebsiella* and *Aerobacter* are resistant.

##### PHARMACOLOGY:

ALPEN *ampicillin* is acid stable and, therefore, well absorbed. Food, however, retards absorption. Blood serum levels of approximately 2 mcg./ml. are attained within 1-2 hours following a 250 mg. oral dose given to fasting adults. Detectable amounts persist for about 6 hours. Ampicillin diffuses readily into all body tissues and fluids with the exception of brain and spinal fluid except when meninges are inflamed. Higher serum levels are obtained following I.M. injection. Most of the ampicillin is excreted unchanged in the urine and this excretion can be delayed by concurrent administration of probenecid. The active form appears in the bile in higher concentrations than found in the serum. Ampicillin is least serum bound of all the penicillin's, averaging about 20% compared to approximately 60%-90% for other penicillins.

##### INDICATIONS

ALPEN *ampicillin* is indicated in the treatment of infections due to susceptible strains of the following: **Gram-Negative Organisms** - *Shigellae*, *Salmonellae* (including *S. typhosa*), *H. influenzae*, *E. coli*, *P. mirabilis*, *N. gonorrhoeae* and *N. meningitidis*. **Gram-Positive Organisms** - Streptococci, *D. pneumoniae*, and nonpenicillinase-producing staphylococci.

Because of its wide spectrum and bactericidal action, it may be useful in instituting therapy; however, bacteriological studies to determine the causative organisms and their sensitivity to ampicillin should be performed.

Indicated surgical procedures should be performed.

##### CONTRAINDICATIONS

The use of this drug is contraindicated in individuals with a history of an allergic reaction to any of the penicillins.

##### WARNINGS

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL THERAPY IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. THESE REACTIONS ARE MORE APT TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR HYPERSENSITIVITY REACTIONS TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE THERAPY WITH A PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, THE DRUG SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE, OXYGEN, INTRAVENOUS STEROIDS, ANY AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

##### USAGE IN PREGNANCY:

Safety for use in pregnancy has not been established.

##### PRECAUTIONS

As with any antibiotic preparation, constant observations for signs of overgrowth of nonsusceptible organisms, including fungi, are essential. Should superinfection occur (usually involving *Aerobacter*, *Pseudomonas*, or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.

As with any potent agent, it is advisable to check periodically for organ system dysfunction during prolonged therapy; this includes renal, hepatic, and hematopoietic systems. This is particularly important in prematures, neonates and other infants.

##### ADVERSE REACTIONS

As with other penicillins, it may be expected that untoward reactions will be essentially limited to sensitivity phenomena. They are more likely to occur in individuals who have previously demonstrated hypersensitivity to penicillins and in those with a history of allergy, asthma, hay fever, or urticaria.

The following adverse reactions have been reported as associated with the use of ampicillin:

**Gastrointestinal** - Glossitis, stomatitis, black "hairy" tongue, nausea, vomiting, diarrhea. (These reactions are usually associated with oral dosage forms.)

\*© 872,458 of Mfr.

**Hypersensitivity Reactions** — An erythematous maculopapular rash has been reported fairly frequently. Urticaria and erythema multiforme have been reported occasionally. A few cases of exfoliative dermatitis have been reported. Anaphylaxis is the most serious reaction experienced and has usually been associated with the parenteral dosage form.

**NOTE:**

Urticaria, other skin rashes, and serum sickness-like reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, ampicillin should be discontinued unless, in the opinion of the physician, the condition being treated is life-threatening and amenable only to ampicillin therapy.

**LIVER** — A moderate rise in serum glutamic oxaloacetic transaminase (SGOT) has been noted, particularly in infants, but the significance of this finding is unknown.

**HEMIC AND LYMPHATIC SYSTEMS** — Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia, and agranulocytosis have been reported during therapy with the penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be sensitivity reactions.

**DOSAGE**

*Infections of the ear, nose, throat, and lower respiratory tract* due to streptococci, pneumococci, and nonpenicillinase-producing staphylococci; and also those infections of the upper and lower respiratory tract due to *H. influenzae*.

Adults: 250 mg. every 6 hours.

Children: 50 mg./kg./day in divided doses every 6 or 8 hours.

*Infections of the genitourinary tract caused by sensitive Gram-negative and Gram-positive bacteria.*

Adults: 500 mg. every 6 hours. Larger doses may be required for severe infections.

Children: 100 mg./kg./day in divided doses every 6 hours.

*Uncomplicated urethritis due to N. gonorrhoeae.*

Adult males and females: 3.5 grams single oral dose administered simultaneously with 1.0 gram of probenecid.

*Cases of gonorrhea with a suspected lesion of syphilis should have dark-field examinations before receiving ampicillin, and monthly serological tests for a minimum of 4 months.*

*Infections of the gastrointestinal tract.*

Adults: 500 mg. every 6 hours.

Children: 100 mg./kg./day in divided doses every 6 hours.

Larger doses may be required for stubborn or severe infections. The children's dosage is intended for individuals whose weight will not cause a dosage to be calculated greater than that recommended for adults. Children weighing more than 20 kg. should be dosed according to the adult recommendations.

It should be recognized that in the treatment of chronic urinary tract and intestinal infections, frequent bacteriological and clinical appraisals are necessary. Smaller doses than those recommended above should not be used. Even higher doses may be needed at times. In stubborn infections, therapy may be required for several weeks. It may be necessary to continue clinical and/or bacteriological follow-up for several months after cessation of therapy.

Treatment should be continued for a minimum of 48 to 72 hours beyond the time that the patient becomes asymptomatic or evidence of bacterial eradication has been obtained. It is recommended that there be at least 10 days' treatment for any infection caused by hemolytic streptococci, to help prevent the occurrence of acute rheumatic fever or glomerulonephritis.

**DIRECTIONS for MIXING ORAL SUSPENSION**

Prepare suspension at time of dispensing as follows: Add the required amount of water (see table below) to the bottle and shake vigorously. Each teaspoonful (5 cc.) will contain 125 mg. or 250 mg. ampicillin.

Bottle Size	Amount of water Required for Reconstitution
80 cc.	53 cc.
100 cc.	66 cc.
150 cc.	100 cc.
200 cc.	132 cc.

**SHAKE WELL BEFORE USING.**

Keep bottle tightly closed. The reconstituted suspension is stable for 7 days at room temperature (70° F) and 14 days under refrigeration (40° F).

**HOW SUPPLIED**

ALPEN ampicillin Capsules. Each capsule contains ampicillin trihydrate equivalent to 250 or 500 mg. ampicillin.

Product No. 3835 250 mg.

Product No. 3836 500 mg.

ALPEN for Oral Suspension. Each 5 cc. of reconstituted oral suspension contains ampicillin trihydrate equivalent to 125 mg. or 250 mg. ampicillin.

125 mg./5 cc. - Product No. 3840, bottles of 80 cc., 100 cc., 150 cc. and 200 cc.

250 mg./5 cc. - Product No. 3841, bottles of 80 cc., 100 cc., 150 cc. and 200 cc.



Manufactured by

**BEECHAM, INC.**

Bristol, Tenn. 37620

For

**LEDERLE LABORATORIES DIVISION**

6953/A

American Cyanamid Company, Pearl River, N.Y. 10965

REV. 10/74

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**Approval Package for:**

**APPLICATION NUMBER:**

**60-666 supplement**

Trade Name: Pen A for Oral Suspension  
125mg/5mL and 250mg/5mL

Generic Name: ampicillin trihydrate

Sponsor: Beecham-Massengill Pharmaceuticals

Approval Date: December 18, 1974

# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:**

**60-666 supplement**

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Reviews / Information Included in this ANDA Review.

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Approval Letter(s)	X
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Microbiology Review(s)	
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**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**APPROVAL LETTER**

1

H-6  
~~Powers~~

# Beecham--Massengill Pharmaceuticals

DIVISION OF BEECHAM INC. CLIFTON, NEW JERSEY

65 INDUSTRIAL SOUTH  
CLIFTON, NEW JERSEY 07012  
REGULATORY DEPARTMENT

**BMP**

CABLE ADDRESS "BEECHPROD"  
TELEX 133471

PHONE: 201-778-9000

*OK to sign out  
JOP 12/18/74*

December 16, 1974

(For use of Food and Drug Administration)

Date approved 12/18/74

Account No. \_\_\_\_\_

Signed John D. ...

Department of Health, Education, and Welfare

Food and Drug Administration  
Div. of Anti-Infective Drug Products  
Certifiable Drug Review Staff (HFD-145)  
Bureau of Drugs  
5600 Fishers Lane  
Rockville, Maryland 20852

Re: #60-666 (440.107c)

Gentlemen:

Reference is made to Beecham-Massengill Pharmaceuticals' approved Form 6 #60-666 covering Ampicillin for Oral Suspension, distributed by Pfizer Inc. under the trade name Pen A.

We are submitting, in triplicate, a final printed insert, which reflects the addition of the manufacturer's identification.

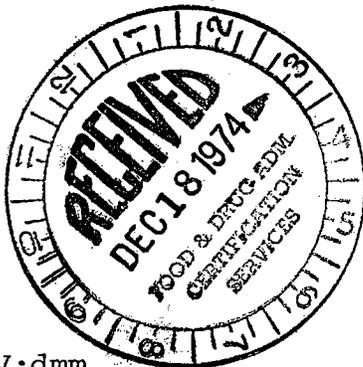
Sincerely,

BEECHAM-MASSENGILL PHARMACEUTICALS

*George Vadnai*

George Vadnai  
Manager, Governmental Affairs

8247



GSV:dmm

Enclosures

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**FINAL PRINTED LABELING**



# Pen A<sup>®</sup>

## ampicillin



	for
CAPSULES	ORAL SUSPENSION
250 mg	125 mg / 5 ml
and	and
500 mg	250 mg / 5 ml

**Description**

Pen A (ampicillin) is derived from the penicillin nucleus, 6-amino-penicillanic acid (6-APA). Chemically it is D (-)  $\alpha$ -aminobenzyl penicillin.

**Actions****MICROBIOLOGY:**

Pen A (ampicillin) is similar to benzyl penicillin in its bactericidal action against sensitive organisms during the stage of active multiplication. It acts through the inhibition of biosynthesis of cell wall mucopeptide. Pen A (ampicillin) differs in *in vitro* spectrum from benzyl penicillin in the gram-negative spectrum. It exerts high *in vitro* activity against many strains of *Hemophilus influenzae*, *Neisseria gonorrhoeae*, *Neisseria meningitidis* and *Neisseria catarrhalis*, *Escherichia coli*, *Proteus mirabilis*, *Bacteroides funduliformis*, *Salmonellae* and *Shigellae*.

*In vitro* studies have also demonstrated the sensitivity of many strains of the following gram-positive bacteria: alpha- and beta-hemolytic streptococci, *Diplococcus pneumoniae*, nonpenicillinase-producing staphylococci, *Bacillus anthracis*, and most strains of enterococci and clostridia. Ampicillin generally provides less *in vitro* activity than penicillin G against gram-positive bacteria. Because it does not resist destruction by penicillinase, it is not effective against penicillinase-producing bacteria, particularly resistant staphylococci. All strains of *Pseudomonas* and most strains of *Klebsiella* and *Aerobacter* are resistant.

**PHARMACOLOGY:**

Pen A (ampicillin) is acid stable and therefore well absorbed. Food, however, retards absorption. Blood serum levels of approximately 2 mcg/ml are attained within 1-2 hours following a 250 mg oral dose given to fasting adults. Detectable amounts persist for about 6 hours. Pen A (ampicillin) diffuses readily into all body tissues and fluids with the exception of brain and spinal fluid except when meninges are inflamed. Higher serum levels are obtained following I.M. injection. Most of the ampicillin is excreted unchanged in the urine and this excretion can be delayed by concurrent administration of probenecid. The active form appears in the bile in higher concentrations than found in the serum. Pen A (ampicillin) is the least serum bound of all the penicillins, averaging about 20% compared to approximately 60%-90% for other penicillins.

**Indications**

Pen A (ampicillin) is indicated in the treatment of infections due to susceptible strains of the following:

*gram-negative organisms*—*Shigellae*, *Salmonellae* (including *S. typhosa*), *H. influenzae*, *E. coli* and *P. mirabilis*, *N. gonorrhoeae*, and *N. meningitidis*;  
*gram-positive organisms*—Streptococci, *D. pneumoniae*, and nonpenicillinase-producing staphylococci.

Because of its wide spectrum and bactericidal action, it may be useful in instituting therapy; however, bacteriological studies to determine the causative organisms and their sensitivity to ampicillin should be performed.

Indicated surgical procedures should be performed.

**Contraindications**

The use of this drug is contraindicated in individuals with a history of an allergic reaction to any of the penicillins.

**Warnings**

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL THERAPY, IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. THESE REACTIONS ARE MORE APT TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR HYPERSENSITIVITY REACTIONS TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE THERAPY WITH A PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, THE DRUG SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED.

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE, OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

**USAGE IN PREGNANCY:**

Safety for use in pregnancy has not been established.

**Precautions**

As with any antibiotic preparation, constant observations for signs of overgrowth of nonsusceptible organisms, including fungi, are essential. Should superinfection occur (usually involving *Aerobacter*, *Pseudomonas*, or *Candida*), the drug should be discontinued and/or appropriate therapy instituted. As with

**Precautions (continued)**

any potent agent, it is advisable to check periodically for organ system dysfunction during prolonged therapy; this includes renal, hepatic, and hematopoietic systems. This is particularly important in prematures, neonates and other infants.

**Adverse Reactions**

As with other penicillins, it may be expected that untoward reactions will be essentially limited to sensitivity phenomena. They are more likely to occur in individuals who have previously demonstrated hypersensitivity to penicillins and in those with a history of allergy, asthma, hay fever, or urticaria. The following adverse reactions have been reported as associated with the use of ampicillin:

**Gastrointestinal**—glossitis, stomatitis, black "hairy" tongue, nausea, vomiting, and diarrhea. (These reactions are usually associated with oral dosage forms.)

**Hypersensitivity reactions**—An erythematous maculopapular rash has been reported fairly frequently. Urticaria and erythema multiforme have been reported occasionally. A few cases of exfoliative dermatitis have been reported. Anaphylaxis is the most serious reaction experienced and has usually been associated with the parenteral dosage form.

**Note:** Urticaria, other skin rashes, and serum sickness-like reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, ampicillin should be discontinued, unless, in the opinion of the physician, the condition being treated is life-threatening and amenable only to ampicillin therapy.

**Liver**—A moderate rise in serum glutamic oxaloacetic transaminase (SGOT) has been noted, particularly in infants, but the significance of this finding is unknown.

**Hemic and Lymphatic Systems**—Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia, and agranulocytosis have been reported during therapy with the penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be sensitivity reactions.

**Dosage**

**Infections of the ear, nose, throat, and lower respiratory tract** due to streptococci, pneumococci, and nonpenicillinase-producing staphylococci, and also those infections of the upper and lower respiratory tract due to *H. influenzae*:

- Adults— 250 mg every 6 hours.
- Children— 50 mg/kg/day in divided doses every 6 or 8 hours.

**Infections of the genitourinary tract caused by sensitive gram-negative and gram-positive bacteria:**

- Adults— 500 mg every 6 hours. Larger doses may be required for severe infections.
- Children— 100 mg/kg/day in divided doses every 6 hours.

**Uncomplicated urethritis due to *N. gonorrhoeae*:**

Adult males and females—3.5 grams single oral dose administered simultaneously with 1.0 gram of probenecid.

Cases of gonorrhoea with a suspected lesion of syphilis should have dark field examinations before receiving ampicillin, and monthly serological tests for a minimum of 4 months.

**Infections of the gastrointestinal tract:**

- Adults— 500 mg every 6 hours.
- Children— 100 mg/kg/day in divided doses every 6 hours.

Larger doses may be required for stubborn or severe infections. The children's dosage is intended for individuals whose weight will not cause a dosage to be calculated greater than that recommended for adults. Children weighing more than 20 kg should be dosed according to the adult recommendations.

It should be recognized that in the treatment of chronic urinary tract and intestinal infections, frequent bacteriological and clinical appraisals are necessary. Smaller doses than those recommended above should not be used. Even higher doses may be needed at times. In stubborn infections, therapy may be required for several weeks. It may be necessary to continue clinical and/or bacteriological follow-up for several months after cessation of therapy.

Treatment should be continued for a minimum of 48 to 72 hours beyond the time that the patient becomes asymptomatic or evidence of bacterial eradication has been obtained. It is recommended that there be at least 10 days' treatment for any infection caused by hemolytic streptococci, to help prevent the occurrence of acute rheumatic fever or glomerulonephritis.

**Directions for Mixing Oral Suspension**

Prepare suspension at time of dispensing as follows: Add 66 ml of water to the 100 ml package and 132 ml of water to the 200 ml package. Shake vigorously. This will provide 100 and 200 ml of suspension, respectively. Each teaspoonful (5 ml) will contain 125 mg or 250 mg ampicillin. SHAKE WELL BEFORE USING. Keep bottle tightly closed. The reconstituted suspension is stable for 7 days at room temperature (70°F.) or 14 days under refrigeration (40°F.).

**How Supplied**

- Pen A (ampicillin) Capsules: Ampicillin trihydrate equivalent to 250 mg or 500 mg ampicillin per capsule.
- 250 mg: bottles of 100, 500, and unit dose (10 x 10's).
- 500 mg: bottles of 100, and unit dose (10 x 10's).
- Pen A (ampicillin) for Oral Suspension: Each 5 ml of reconstituted suspension contains ampicillin trihydrate equivalent to 125 mg or 250 mg ampicillin.
- 125 mg/5 ml: bottles of 100 ml and 200 ml.
- 250 mg/5 ml: bottles of 100 ml and 200 ml.

Manufactured by Beecham Inc., Bristol, TN 37620

Distributed by  
**PFIZER LABORATORIES DIVISION**  
PFIZER INC.

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**Approval Package for:**

**APPLICATION NUMBER:**

**60-666 supplement**

Generic Name: Ampicillin Trihydrate for Oral  
Suspension, 125mg/5mL & 250mg/5mL

Sponsor: Beecham-Massengill Pharmaceuticals

Approval Date: February 21, 1975

# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:**

**60-666 supplement**

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**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**APPROVAL LETTER**

17-6  
Harrison

# Beecham-Massengill Pharmaceuticals

DIVISION OF BEECHAM INC. CLIFTON, NEW JERSEY



65 INDUSTRIAL SOUTH  
CLIFTON, NEW JERSEY 07012  
REGULATORY DEPARTMENT

CABLE ADDRESS "BEECHPROD"  
TELEX 133471

PHONE: 201-778-9000

February 13, 1975

Date Approved: 2/21/75

Food and Drug Administration  
Certifiable Drug Review Staff (HFD-535)  
Div. of Generic Drug Monographs  
Bureau of Drugs  
5600 Fishers Lane  
Rockville, Maryland 20852

*John D. Harrison*  
Director

Re: #60-666 (440.107c)

Gentlemen:

Reference is made to Beecham Laboratories' approved Form 6 Antibiotic Application (#60-666) for Ampicillin Trihydrate for Oral Suspension.

We hereby wish to supplement our Application to provide for an updated Product Specification and Manufacturing Directions which contain minor revisions and code number and editorial changes.

This supplement is submitted in triplicate.

9202



Sincerely,

BEECHAM LABORATORIES

*George Vadnai*

George Vadnai  
Manager, Governmental Affairs

GSV:dmm

Enclosures

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**Approval Package for:**

**APPLICATION NUMBER:**

**60-666 supplement**

Trade Name: Totacillin for Oral Suspension  
125mg/5mL and 250mg/5mL

Generic Name: ampicillin trihydrate

Sponsor: Beecham Laboratories

Approval Date: July 28, 1975

# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:**

**60-666 supplement**

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Reviews / Information Included in this ANDA Review.

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Chemistry Review(s)	
Microbiology Review(s)	
Bioequivalence Review(s)	
Administrative Document(s)	X
Correspondence	X

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**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**APPROVAL LETTER**

ack me 7/28/75 A-6  
~~Eisler~~

# Beecham laboratories

65 INDUSTRIAL SOUTH, CLIFTON, NEW JERSEY 07012 201-778-9000

REGULATORY DEPARTMENT

CABLE ADDRESS "BEECHPROD"  
TELEX 133471

June 4, 1975 **Date Approved** 7/28/75

**Account No.**  
**Signed** *[Signature]*  
**For The** **Department of Health and Drug Administration**  
**Department of Health and Welfare**

Food and Drug Administration  
Certifiable Drug Review Staff (HFD-535)  
Bureau of Drugs  
5600 Fishers Lane  
Rockville, Maryland 20852

Re: #60-666 (440,107c)

Gentlemen:

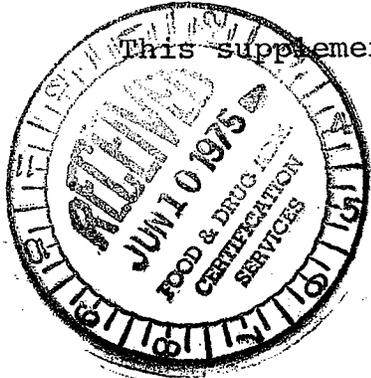
Reference is made to Beecham Laboratories' Form 6 Anti-biotic Application for Totacillin (ampicillin) for Oral Suspension 125 mg./5 ml. and 250 mg./5 ml. We hereby wish to supplement our Application to provide additional stability data (36 months plus 12 months comparative supporting data for metal vs. caps); and request the extension of the expiry date to 36 months.

Under separate cover, the following samples are being transmitted:

6 bottles	125 mg./5 ml.	Lot #498 - 53862
6 bottles	125 mg./5 ml.	#499 - 53863
6 bottles	250 mg./5 ml.	#500 - 53864
6 bottles	250 mg./5 ml.	#501 - 53865

In accordance with our discussions with Mr. Eisler, future stability data will include both volume and weight based assays. Since the enclosed data was developed before our agreement, it contains assay results on the "per 5 ml." basis only.

This supplement is submitted in triplicate.



11037

Sincerely,

BEECHAM LABORATORIES

*[Signature]*

George Vadnai  
Manager, Governmental Affairs

GSV:dmm  
Enclosures

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**ADMINISTRATIVE  
DOCUMENT(S)**

MEMO RECORD	AVOID ERRORS PUT IT IN WRITING	DATE JUNE 11, 1975
FROM: MILTON FISLER HFD - 535	OFFICE	
TO: BERNARD ARRET HFD - 431	DIVISION OF GENERIC DRUG MONOGRAPHS	
SUBJECT: BEECHAM LABORATORIES - AMPICILLIN		
SUMMARY TRIHYDRATE FOR ORAL SUSPENSION, 125 mg/5ml + 250 mg/5ml - REQUEST EXTENSION OF EXPIRATION DATE TO THIRTY-SIX (36) MONTHS		
Beecham has submitted data from a number of batches and samples from 7 aged batches		
Please test <u>all</u> batches		
① Do potency when reconstituted		
② "refrigerated" for 14 days and		
③ Do any additional monograph tests		
you feel may be necessary.		
<u>Note</u>		
ⓐ - Resuspendability		
ⓑ - Closure integrity following reconstitution and shaking		
<u>Enclosed</u>		
① Samples		
② submission dated June 4, 1975		
SIGNATURE Milton	DOCUMENT NUMBER 60-666 (40107c)	

MEMO RECORD	AVOID ERRORS PUT IT IN WRITING	DATE 7-23-75						
FROM: <i>Lola H. Wayland</i>		OFFICE <i>PRT</i>						
TO: <i>Milton Eisler thru B. Arret DA</i>		DIVISION <i>NCAA</i>						
SUBJECT: <i>Beecham Aspirinoids.</i>								
<p data-bbox="248 415 345 432">SUMMARY</p> <p data-bbox="248 441 1542 787">The 3 remaining bottles of S 2864 (lot #500) were reconstituted as directed and the potency checked by the <u>                    </u> auto-analytical procedure. The results appear below and are satisfactory.</p> <table data-bbox="487 819 698 1029"> <tr> <td><i>1</i></td> <td><i>274</i></td> </tr> <tr> <td><i>2</i></td> <td><i>273</i></td> </tr> <tr> <td><i>3</i></td> <td><i>271</i></td> </tr> </table> <p data-bbox="438 1039 1234 1186"><i>aw<sub>3</sub> = 272.7 mg/ml</i> <i>                    % of label claim.</i></p> <p data-bbox="771 1396 1063 1501"><b>APPEARS THIS WAY ON ORIGINAL</b></p>			<i>1</i>	<i>274</i>	<i>2</i>	<i>273</i>	<i>3</i>	<i>271</i>
<i>1</i>	<i>274</i>							
<i>2</i>	<i>273</i>							
<i>3</i>	<i>271</i>							
SIGNATURE	DOCUMENT NUMBER <i>60-666</i>							

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**CORRESPONDENCE**



DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE  
 PUBLIC HEALTH SERVICE  
 FOOD AND DRUG ADMINISTRATION  
 ROCKVILLE, MARYLAND 20852

Our Reference: 60-666 (440.107c)

Date: July 28, 1975

LETTER OF APPROVAL--Extension  
 Of Expiration Date

Your request dated: June 4, 1975

RE: Your Batchmark No.	FDA No.
498	S2862
499	S2863
500	S2864
501	S2865

George Vadnai  
 Manager, Governmental Affairs  
 Beecham Laboratories  
 65 Industrial South  
 Clifton, New Jersey 07012

Dear Mr. Vadnai:

Our laboratories have completed testing samples from the above-referenced aged batches. On the basis of the data available to us at this time we believe your proposal to extend the expiration date on future batches of the referenced product has been adequately substantiated.

BEECHAM LABORATORIES is hereby authorized to use an expiration date of 36 months on all new batches of Ampicillin Trihydrate for Oral Suspension 125 mg./5ml and 250 mg./5 ml, manufactured and packaged in accord with approved Form 6 specifications. (Detail generic name, potency[ies], type packaging, submitted for certification testing after the date of this letter. An approved copy of your request for the new dating period is enclosed for your records.

The fees charged for conducting the confirmatory tests and assays in our laboratories are indicated on the enclosed copies of FDA Form 1687. Your antibiotic certification account number 576 will be billed in the usual manner for such tests performed in the amount of \$ 420.00.

Sincerely,

Milton Eisler  
 Consumer Safety Officer  
 Certifiable Drug Review Staff (HFD-535)  
 Division of Generic Drug Monographs

cc: NWK-DO  
 HFD-535  
 HFD-535/OD  
 HFD-430/lab.  
 K. Whitley HFD-332  
 e Clerk  
 isler:hb

Enclosures

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**Approval Package for:**

**APPLICATION NUMBER:**

**60-666 supplement**

Trade Name: Alpen for Oral Suspension  
125mg/5mL and 250mg/5mL

Generic Name: ampicillin trihydrate

Sponsor: Beecham Laboratories

Approval Date: September 4, 1975

# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:**

**60-666 supplement**

## CONTENTS

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Reviews / Information Included in this ANDA Review.

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Approval Letter(s)	X
Tentative Approval Letter(s)	
Final Printed Labeling	X
CSO Labeling Review(s)	
Medical Officer Review(s)	
Chemistry Review(s)	
Microbiology Review(s)	
Bioequivalence Review(s)	
Administrative Document(s)	
Correspondence	

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**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**APPROVAL LETTER**

①

A-6  
~~XXXXXX~~

# Beecham laboratories

65 INDUSTRIAL SOUTH, CLIFTON, NEW JERSEY 07012

201-778-9000

REGULATORY DEPARTMENT

CABLE ADDRESS "BEECHPROD"  
TELEX 133471

*ok to payment  
9/4/75*

August 21, 1975

Food and Drug Administration  
Certifiable Drug Review Staff (HFD-525) Bc  
Division of Generic Drug Monographs  
Bureau of Drugs  
5600 Fishers Lane  
Rockville, Maryland 20852

(For use of Food and Drug Administration)

Date approved 9/4/75

Signed John O. Garrison

For the Commissioner of Food and Drugs  
Food and Drug Administration  
Department of Health, Education and Welfare

Re: #60-666 (440.107C)

Gentlemen:

Reference is made to Beecham Laboratories' approved Form 6 #60-666, covering Ampicillin for Oral Suspension, distributed by Lederle Laboratories under the trade name Alpen.

We are submitting, in triplicate, final printed labeling which reflects the addition of the manufacturer's identification.



Sincerely,

BEECHAM LABORATORIES

*G. Vadnai*

George Vadnai  
Manager, Regulatory Affairs

12086

GSV:sc  
enclosures

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**FINAL PRINTED LABELING**

71093  
D9

# ALPEN\*

## AMPICILLIN

### for Oral Use

#### DESCRIPTION

ALPEN *ampicillin* is derived from the penicillin nucleus, 6-aminopenicillanic acid (6-APA). Chemically it is D (-)  $\alpha$ -aminobenzylpenicillin trihydrate.

#### ACTIONS

##### MICROBIOLOGY:

Ampicillin is similar to benzyl penicillin in its bactericidal action against sensitive organisms during the stage of active multiplication. It acts through the inhibition of biosynthesis of cell wall mucopeptide. Ampicillin differs in *in vitro* spectrum from benzylpenicillin in the Gram-negative spectrum. It exerts high *in vitro* activity against many strains of *Haemophilus influenzae*, *Neisseria gonorrhoeae*, *Neisseria meningitidis* and *Neisseria catarrhalis*, *Escherichia coli*, *Proteus mirabilis*, *Bacteroides funduliformis*, *Salmonellae*, and *Shigellae*.

*In vitro* studies have also demonstrated the sensitivity of many strains of the following Gram-positive bacteria: alpha- and beta-hemolytic streptococci, *Diplococcus pneumoniae*, nonpenicillinase-producing staphylococci, *Bacillus anthracis*, and most strains of enterococci and clostridia. Ampicillin generally provides less *in vitro* activity than penicillin-G against Gram-positive bacteria. Because it does not resist destruction by penicillinase it is *not* effective against penicillinase-producing bacteria, particularly resistant staphylococci. All strains of *Pseudomonas* and most strains of *Klebsiella* and *Aerobacter* are resistant.

##### PHARMACOLOGY:

ALPEN *ampicillin* is acid stable and, therefore, well absorbed. Food, however, retards absorption. Blood serum levels of approximately 2 mcg/ml are attained within 1-2 hours following a 250 mg oral dose given to fasting adults. Detectable amounts persist for about 6 hours. Ampicillin diffuses readily into all body tissues and fluids with the exception of brain and spinal fluid except when meninges are inflamed. Higher serum levels are obtained following I.M. injection. Most of the ampicillin is excreted unchanged in the urine and this excretion can be delayed by concurrent administration of probenecid. The active form appears in the bile in higher concentrations than found in the serum. Ampicillin is least serum bound of all the penicillins, averaging about 20% compared to approximately 60%-90% for other penicillins.

##### INDICATIONS

ALPEN *ampicillin* is indicated in the treatment of infections due to susceptible strains of the following: **Gram-Negative Organisms** - *Shigellae*, *Salmonellae* (including *S. typhosa*), *H. influenzae*, *E. coli*, *P. mirabilis*, *N. gonorrhoeae* and *N. meningitidis*. **Gram-Positive Organisms** - Streptococci, *D. pneumoniae*, and nonpenicillinase-producing staphylococci.

Because of its wide spectrum and bactericidal action, it may be useful in instituting therapy; however, bacteriological studies to determine the causative organisms and their sensitivity to ampicillin should be performed.

Indicated surgical procedures should be performed.

#### CONTRAINDICATIONS

The use of this drug is contraindicated in individuals with a history of an allergic reaction to any of the penicillins.

#### WARNINGS

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL THERAPY IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. THESE REACTIONS ARE MORE APT TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR HYPERSENSITIVITY REACTIONS TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE THERAPY WITH A PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, THE DRUG SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE, OXYGEN, INTRAVENOUS STEROIDS, ANY AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

#### USAGE IN PREGNANCY:

Safety for use in pregnancy has not been established.

#### PRECAUTIONS

As with any antibiotic preparation, constant observations for signs of overgrowth of nonsusceptible organisms, including fungi, are essential. Should superinfection occur (usually involving *Aerobacter*, *Pseudomonas*, or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.

As with any potent agent, it is advisable to check periodically for organ system dysfunction during prolonged therapy; this includes renal, hepatic, and hematopoietic systems. This is particularly important in prematures, neonates and other infants.

#### ADVERSE REACTIONS

As with other penicillins, it may be expected that untoward reactions will be essentially limited to sensitivity phenomena. They are more likely to occur in individuals who have previously demonstrated hypersensitivity to penicillins and in those with a history of allergy, asthma, hay fever, or urticaria.

The following adverse reactions have been reported as associated with the use of ampicillin:  
**Gastrointestinal** - Glossitis, stomatitis, black "hairy" tongue, nausea, vomiting, diarrhea. (These reactions are usually associated with oral dosage forms.)

\*© 872,458 of Mfr.

**Hypersensitivity Reactions** — An erythematous maculopapular rash has been reported fairly frequently. Urticaria and erythema multiforme have been reported occasionally. A few cases of exfoliative dermatitis have been reported. Anaphylaxis is the most serious reaction experienced and has usually been associated with the parenteral dosage form.

**NOTE:**

Urticaria, other skin rashes, and serum sickness-like reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, ampicillin should be discontinued unless, in the opinion of the physician, the condition being treated is life-threatening and amenable only to ampicillin therapy.

**LIVER** — A moderate rise in serum glutamic oxaloacetic transaminase (SGOT) has been noted, particularly in infants, but the significance of this finding is unknown.

**HEMIC AND LYMPHATIC SYSTEMS** — Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia, and agranulocytosis have been reported during therapy with the penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be sensitivity reactions.

**DOSAGE**

*Infections of the ear, nose, throat, and lower respiratory tract due to streptococci, pneumococci, and nonpenicillinase-producing staphylococci; and also those infections of the upper and lower respiratory tract due to H. influenzae.*

Adults: 250 mg every 6 hours.  
Children: 50 mg/kg/day in divided doses every 6 or 8 hours.

*Infections of the genitourinary tract caused by sensitive Gram-negative and Gram-positive bacteria.*

Adults: 500 mg every 6 hours. Larger doses may be required for severe infections.  
Children: 100 mg/kg/day in divided doses every 6 hours.

*Uncomplicated urethritis due to N. gonorrhoeae.*

Adult males and females: 3.5 grams single oral dose administered simultaneously with 1.0 gram of probenecid.

*Cases of gonorrhea with a suspected lesion of syphilis should have dark-field examinations before receiving ampicillin, and monthly serological tests for a minimum of 4 months.*

*Infections of the gastrointestinal tract.*

Adults: 500 mg every 6 hours.  
Children: 100 mg/kg/day in divided doses every 6 hours.

Larger doses may be required for stubborn or severe infections. The children's dosage is intended for individuals whose weight will not cause a dosage to be calculated greater than that recommended for adults. Children weighing more than 20 kg should be dosed according to the adult recommendations.

It should be recognized that in the treatment of chronic urinary tract and intestinal infections, frequent bacteriological and clinical appraisals are necessary. Smaller doses than those recommended above should not be used. Even higher doses may be needed at times. In stubborn infections, therapy may be required for several weeks. It may be necessary to continue clinical and/or bacteriological follow-up for several months after cessation of therapy.

Treatment should be continued for a minimum of 48 to 72 hours beyond the time that the patient becomes asymptomatic or evidence of bacterial eradication has been obtained. It is recommended that there be at least 10 days' treatment for any infection caused by hemolytic streptococci, to help prevent the occurrence of acute rheumatic fever or glomerulonephritis.

**DIRECTIONS for MIXING ORAL SUSPENSION**

Prepare suspension at time of dispensing as follows: Add the required amount of water (see table below) to the bottle and shake vigorously. Each teaspoonful (5 ml) will contain 125 mg or 250 mg ampicillin.

Bottle Size	Amount of water Required for Reconstitution
80 ml	53 ml
100 ml	66 ml
150 ml	100 ml
200 ml	132 ml

**SHAKE WELL BEFORE USING.**

Keep bottle tightly closed. The reconstituted suspension is stable for 7 days at room temperature (70°F) and 14 days under refrigeration (40°F).

**HOW SUPPLIED**

ALPEN ampicillin Capsules. Each capsule contains ampicillin trihydrate equivalent to 250 or 500 mg ampicillin.

Product No. 3835 250 mg  
Product No. 3836 500 mg

ALPEN for Oral Suspension: Each 5 ml of reconstituted oral suspension contains ampicillin trihydrate equivalent to 125 mg or 250 mg ampicillin.

125 mg/5 ml - Product No. 3840, bottles of 80 ml, 100 ml, 150 ml and 200 ml  
250 mg/5 ml - Product No. 3841, bottles of 80 ml, 100 ml, 150 ml and 200 ml



Manufactured by  
**BEECHAM LABORATORIES**  
Division of Beecham Inc.  
Bristol, Tenn. 37620  
For

**LEDERLE LABORATORIES DIVISION**

6953/B

American Cyanamid Company, Pearl River, N.Y. 10965

REV. 6/75

*For Your Information and File*  
 THIS FACSIMILE OF TEXT IS THE LATEST PRINTING

Product No. \_\_\_\_\_

Package No. \_\_\_\_\_

Text Code No. \_\_\_\_\_

Date \_\_\_\_\_

Kind of Labeling \_\_\_\_\_

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LPR 269A REV. 4/63

**KEEP TIGHTLY CLOSED  
 SHAKE WELL BEFORE USING**  
 When stored at room temperature discard unused portion after 7 days.  
 When stored under refrigeration discard unused portion after 14 days.  
 Control No. \_\_\_\_\_ Date Reconstituted \_\_\_\_\_



**Alpen\***  
**Ampicillin**  
 for  
**Oral Suspension**

equivalent to 2.0 Grams Ampicillin

Cherry Flavored

When Reconstituted Each 5 ml contains Ampicillin Trihydrate equivalent to

**125 mg** Ampicillin

CAUTION: Federal law prohibits dispensing without prescription.

**80 ml**(when reconstituted)



Exp. Date \_\_\_\_\_

**Directions for Mixing  
 Prior to Dispensing:**  
 Loosen powder, add a total of 53 ml of water in two portions and shake well after each addition.

**EACH 5 ml CONTAINS:**  
 Ampicillin trihydrate equivalent to 125 mg Ampicillin.

**USUAL DOSAGE:**

**CHILDREN:**  
 50-100 mg/kg/day in divided doses every 6-8 hours.

**ADULTS:**  
 250-500 mg every 6 hours.

**IMPORTANT:**  
 Read accompanying literature for indications, dosage and precautions.

Manufactured by  
**BEECHAM LABORATORIES**  
 Division of Beecham Inc.  
 Bristol, Tenn. 37620  
 for  
**LEDERLE LABORATORIES**  
 DIVISION  
 American Cyanamid Company  
 Pearl River, N.Y. 10965

6956/A

*For Your Information and File*  
 THIS FACSIMILE OF TEXT IS THE LATEST PRINTING

Product No. \_\_\_\_\_

Package No. \_\_\_\_\_

Text Code No. \_\_\_\_\_

Date \_\_\_\_\_

Kind of Labeling \_\_\_\_\_

position No. \_\_\_\_\_



**Alpen\***  
**Ampicillin**  
 for  
**Oral Suspension**

equivalent to 2.5 Grams Ampicillin

**Cherry Flavored**

When Reconstituted Each 5 ml contains Ampicillin Trihydrate equivalent to

**125 mg** Ampicillin

CAUTION: Federal law prohibits dispensing without prescription.

**100 ml** (when reconstituted)



**Directions for Mixing Prior to Dispensing:**  
 Loosen powder, add a total of 66 ml of water in two portions and shake well after each addition.

**EACH 5 ml CONTAINS:**  
 Ampicillin trihydrate equivalent to 125 mg Ampicillin.

**USUAL DOSAGE:**  
**CHILDREN:**  
 50-100 mg/kg/day in divided doses every 6-8 hours.

**ADULTS:**  
 250-500 mg every 6 hours.

**IMPORTANT:**  
 Read accompanying literature for indications, dosage and precautions.

Manufactured by  
 BEECHAM LABORATORIES  
 Division of Beecham Inc.  
 Bristol, Tenn. 37620  
 for  
 LEDERLE LABORATORIES  
 DIVISION  
 American Cyanamid Company  
 Pearl River, N.Y. 10965

**KEEP TIGHTLY CLOSED  
 SHAKE WELL BEFORE USING**

When stored at room temperature discard unused portion after 7 days; when stored under refrigeration discard unused portion after 14 days.  
 Control No. \_\_\_\_\_ Date Reconstituted \_\_\_\_\_

Exp. Date \_\_\_\_\_

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*For Your Information and File*  
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Product No. \_\_\_\_\_  
 Package No. \_\_\_\_\_  
 Text Code No. \_\_\_\_\_  
 Date \_\_\_\_\_  
 Kind of Labeling \_\_\_\_\_



**Alpen\***  
**Ampicillin**  
 for  
**Oral Suspension**

equivalent to 3.75 Grams Ampicillin  
**Cherry Flavored**  
 When Reconstituted Each 5 ml  
 contains Ampicillin Trihydrate  
 equivalent to

**125 mg** Ampicillin

CAUTION: Federal law prohibits  
 dispensing without prescription.

**150 ml** (when reconstituted)



**KEEP TIGHTLY CLOSED**  
**SHAKE WELL BEFORE USING**  
 When stored at room temperature discard unused portion after 7 days;  
 when stored under refrigeration discard unused portion after 14 days.  
 Control No. \_\_\_\_\_ Date Reconstituted \_\_\_\_\_

Exp. Date \_\_\_\_\_

Directions for Mixing  
 Prior to Dispensing:  
 Loosen powder, add a total of  
 100 ml of water in two portions  
 and shake well after each addition.

**EACH 5 ml CONTAINS:**  
 Ampicillin trihydrate equivalent  
 to 125 mg Ampicillin.

**USUAL DOSAGE:**  
**CHILDREN:**  
 50-100 mg/kg/day in divided doses  
 every 6-8 hours.

**ADULTS:**  
 250-500 mg every 6  
 hours.

**IMPORTANT:**  
 Read accompanying literature for  
 indications, dosage and  
 precautions.

Manufactured by  
**BEECHAM LABORATORIES**  
 Division of Beecham, Inc.  
 Bristol, Tenn. 37620  
 for  
**LEDERLE LABORATORIES**  
 DIVISION  
 American Cyanamid Company  
 Pearl River, N.Y. 10965

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*For Your Information and File*  
 THIS FACSIMILE OF TEXT IS THE LATEST PRINTING

**KEEP TIGHTLY CLOSED  
 SHAKE WELL BEFORE USING**  
 When stored at room temperature, discard unused portion after 7 days.  
 When stored under refrigeration, discard unused portion after 14 days.  
 Control No. \_\_\_\_\_ Date Reconstituted \_\_\_\_\_

Exp. Date \_\_\_\_\_



**Alpen\***  
**Ampicillin**  
 for  
**Oral Suspension**

equivalent to 4.0 Grams Ampicillin  
**Cherry Flavored**  
 When Reconstituted Each 5 ml  
 contains Ampicillin Trihydrate  
 equivalent to

**250 mg** Ampicillin

CAUTION: Federal law prohibits  
 dispensing without prescription.

**80 ml**(when reconstituted)



**Directions for Mixing**  
 Prior to Dispensing:  
 Loosen powder, add a total of  
 53 ml of water in two portions  
 and shake well after each  
 addition.

**EACH 5 ml CONTAINS:**  
 Ampicillin trihydrate equivalent  
 to 250 mg Ampicillin.

**USUAL DOSAGE:**  
**CHILDREN:**  
 50-100 mg/kg/day in divided doses  
 every 6-8 hours.

**ADULTS:**  
 250-500 mg every 6  
 hours.

**IMPORTANT:**  
 Read accompanying literature for  
 indications, dosage and  
 precautions.

Manufactured by  
**BEECHAM LABORATORIES**  
 Division of Beecham Inc.  
 Bristol, Tenn., 37620

for  
**LEDERLE LABORATORIES**  
 DIVISION  
 American Cyanamid Company  
 Pearl River, N.Y. 10965

Product No. \_\_\_\_\_

Package No. \_\_\_\_\_

Text Code No. \_\_\_\_\_

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Kind of Labeling \_\_\_\_\_

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Grain Direction \_\_\_\_\_

*For Your Information and File*  
 THIS FACSIMILE OF TEXT IS THE LATEST PRINTING

Product No. \_\_\_\_\_  
 Package No. \_\_\_\_\_  
 Text Code No. \_\_\_\_\_  
 Date \_\_\_\_\_  
 Kind of Labeling \_\_\_\_\_  
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**Alpen\***  
**Ampicillin**  
 for  
**Oral Suspension**

equivalent to 5.0 Grams Ampicillin

**Cherry Flavored**

When Reconstituted Each 5 ml contains Ampicillin Trihydrate equivalent to

**250 mg** Ampicillin

CAUTION: Federal law prohibits dispensing without prescription.

**100 ml** (when reconstituted)



**Directions for Mixing**  
 Prior to Dispensing:  
 Loosen powder, add a total of 65 ml of water in two portions and shake well after each addition.

**EACH 5 ml CONTAINS:**  
 Ampicillin trihydrate equivalent to 250 mg Ampicillin.

**USUAL DOSAGE:**  
**CHILDREN:**  
 50-100 mg/kg/day in divided doses every 6-8 hours.

**ADULTS:**  
 250-500 mg every 6 hours.

**IMPORTANT:**  
 Read accompanying literature for indications, dosage and precautions.

Manufactured by  
**BEECHAM LABORATORIES**  
 Division of Beecham Inc.  
 Bristol, Tenn. 37620  
 for  
**LEDERLE LABORATORIES**  
 DIVISION  
 American Cyanamid Company  
 Pearl River, N.Y. 10965

**KEEP TIGHTLY CLOSED**  
**SHAKE WELL BEFORE USING**

When stored at room temperature discard unused portion after 7 days;  
 when stored under refrigeration discard unused portion after 14 days.  
 Control No. \_\_\_\_\_ Date Reconstituted \_\_\_\_\_

Exp. Date \_\_\_\_\_

Book

\_\_\_\_\_ Tint Size

\_\_\_\_\_ Tail Size

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\_\_\_\_\_ Y \_\_\_\_\_

\_\_\_\_\_ or Jar \_\_\_\_\_

Grain Direction \_\_\_\_\_

*For Your Information and File*  
 THIS FACSIMILE OF TEXT IS THE LATEST PRINTING

Product No. \_\_\_\_\_  
 Package No. \_\_\_\_\_  
 Text Code No. \_\_\_\_\_  
 Date \_\_\_\_\_  
 Kind of Labeling \_\_\_\_\_

**KEEP TIGHTLY CLOSED  
 SHAKE WELL BEFORE USING**  
 When stored at room temperature discard unused portion after 7 days;  
 when stored under refrigeration discard unused portion after 14 days.  
 See package insert for complete directions. Date Reconstituted  
 Control No.



**Alpen\***  
**Ampicillin**  
 for  
**Oral Suspension**

equivalent to 7.5 Grams Ampicillin

**Cherry Flavored**

When Reconstituted Each 5 ml  
 contains Ampicillin Trihydrate  
 equivalent to

**250 mg** Ampicillin

CAUTION: Federal law prohibits  
 dispensing without prescription.

**150 ml** (when reconstituted)

Exp. Date

**Directions for Mixing**  
**Prior to Dispensing:**  
 Loosen powder, add a total of  
 100 ml of water in two portions  
 and shake well after each addition.

**EACH 5 ml CONTAINS:**  
 Ampicillin trihydrate equivalent  
 to 250 mg Ampicillin.

**USUAL DOSAGE:**  
**CHILDREN:**  
 50-100 mg/kg/day in divided doses  
 every 6-8 hours.

**ADULTS:**  
 250-500 mg every 6  
 hours.

**IMPORTANT:**  
 Read accompanying literature for  
 indications, dosage and  
 precautions.

Manufactured by  
**BEECHAM LABORATORIES**  
 Division of Beecham Inc.  
 Bristol, Tenn. 37620

for  
**LEDERLE LABORATORIES**  
 DIVISION  
 American Cyanamid Company  
 Pearl River, N.Y. 10965

6962/A

Position No. \_\_\_\_\_

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Box or Jar \_\_\_\_\_

Grain Direction \_\_\_\_\_

*For Your Information and File*  
 THIS FACSIMILE OF TEXT IS THE LATEST PRINTING

**KEEP TIGHTLY CLOSED  
 SHAKE WELL BEFORE USING**

When stored at room temperature discard unused portion after 7 days;  
 when stored under refrigeration discard unused portion after 14 days.

Control No. \_\_\_\_\_  
 Date Reconstituted \_\_\_\_\_

Exp. Date \_\_\_\_\_



**Alpen\***  
**Ampicillin**  
 for  
**Oral Suspension**

equivalent to 10.0 Grams Ampicillin

**Cherry Flavored**

When Reconstituted Each 5 ml contains Ampicillin Trihydrate equivalent to

**250 mg** Ampicillin

CAUTION: Federal law prohibits dispensing without prescription.

**200 ml** (when reconstituted)



**Directions for Mixing  
 Prior to Dispensing:**  
 Loosen powder, add a total of 132 ml of water in two portions and shake well after each addition.

**EACH 5 ml CONTAINS:**  
 Ampicillin trihydrate equivalent to 250 mg Ampicillin.

**USUAL DOSAGE:**  
**CHILDREN:**  
 50-100 mg/kg/day in divided doses every 6-8 hours.

**ADULTS:**  
 250-500 mg every 6 hours.

**IMPORTANT:**  
 Read accompanying literature for indications, dosage and precautions.

Manufactured by  
**BEECHAM LABORATORIES**  
 Division of Beecham Inc.  
 Bristol, Tenn. 37620  
 for  
**LEDERLE LABORATORIES**  
 DIVISION  
 American Cyanamid Company  
 Pearl River, N.Y. 10965

Product No. \_\_\_\_\_

Package No. \_\_\_\_\_

Text Code No. \_\_\_\_\_

Date \_\_\_\_\_

Kind of Labeling \_\_\_\_\_

6963/A  
 Proposition No. \_\_\_\_\_

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**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**Approval Package for:**

**APPLICATION NUMBER:**

**60-666 supplement**

Trade Name: Penbritin for Oral Suspension  
125mg/5mL and 250mg/5mL

Generic Name: ampicillin trihydrate

Sponsor: Beecham Laboratories

Approval Date: November 12, 1975

# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:**

**60-666 supplement**

## CONTENTS

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Medical Officer Review(s)	
Chemistry Review(s)	
Microbiology Review(s)	
Bioequivalence Review(s)	
Administrative Document(s)	
Correspondence	

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**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**APPROVAL LETTER**

**Beecham**  
laboratories

65 INDUSTRIAL SOUTH, CLIFTON, NEW JERSEY 07012

201-778-9000

REGULATORY DEPARTMENT

CABLE ADDRESS "BEECHPROD"  
TELEX 133471

November 7, 1975

Date Approved 11/12/75

Account No. \_\_\_\_\_

Signed *John D. Harrison*

For the Com. \_\_\_\_\_

Department \_\_\_\_\_

Food and Drug Administration  
Certifiable Drug Review Staff (HFD-535)  
Div. of Generic Drug Monographs  
Bureau of Drugs  
5600 Fishers Lane  
Rockville, Maryland 20852

Re: #60-666 (440.107c)

Gentlemen:

Reference is made to Beecham Laboratories' approved Form 6 Antibiotic Application #60-666 covering Ampicillin for Oral Suspension, distributed by Ayerst Laboratories Inc. under the trade name Penbritin.

We are hereby submitting, in triplicate, a final printed package insert revised to delete the manufacturer's name and final printed labels which add the manufacturer's name.

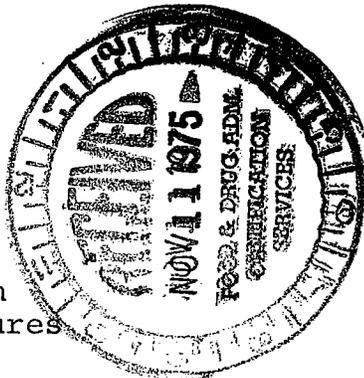
Sincerely,

BEECHAM LABORATORIES

*G. Vadnai*

George Vadnai  
Manager, Governmental Affairs

01288



GSV:dmm  
Enclosures

*A-6*  
~~*Powers*~~

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**FINAL PRINTED LABELING**

Note: No refrigeration required before mixing. After mixing, suspension may be kept at room temperature for 7 days or in a refrigerator for 14 days without significant loss of potency.

**SHAKE WELL BEFORE USING • KEEP TIGHTLY CLOSED**

Control No. \_\_\_\_\_ (Tear along dotted line.)  
Exp. Date \_\_\_\_\_

Directions for mixing: Add 66 cc. of water and shake vigorously. Each 5 cc. (one teaspoonful) will then contain 25 mg. of ampicillin in a pleasant cherry-flavored suspension.



2.5 Gm.  
Ampicillin  
100 cc.  
(When  
mixed)

When reconstituted,  
each 5 cc. contains  
**125 mg.**  
ampicillin as  
the trihydrate.



CAUTION: Federal law prohibits dispensing without prescription.

Usual dosage—10 mg./kg./day, in divided doses every 6-8 hours.  
Children: 50-100 mg. every 6 hours. See accompanying literature.  
Adults: 250-500 mg. every 6 hours. See accompanying literature.

Manufactured by Beecham Laboratories,  
Div. of Beecham Inc., Bristol, Tenn. 37620

Distributed by  
**AYERST LABORATORIES INCORPORATED**  
NEW YORK, N.Y. 10017

\*Nfr. U.S. under # 705,484. 6349C Made in U.S.A.

**Note:** No refrigeration required before mixing. After mixing, suspension may be kept at room temperature for 7 days or in a refrigerator for 14 days without significant loss of potency.

**SHAKE WELL BEFORE USING • KEEP TIGHTLY CLOSED**

Control No.

Exp. Date

(Tear along dotted line.)

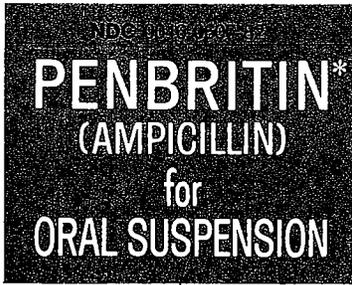
**Directions for mixing:** Add 122 cc. of water and shake vigorously. Each 5 cc. (one teaspoonful) will then contain 125 mg. of ampicillin in a pleasant cherry-flavored suspension.

**Ayerst**

5 Gm.  
Ampicillin  
200 cc.  
(When  
mixed)

CAUTION: Federal law  
prohibits dispensing  
without prescription.

When reconstituted,  
each 5 cc. contains  
**125 mg.**  
ampicillin as  
the trihydrate.



**Usual dosage—**  
Children: 50-100 mg./kg./day in divided doses every 6-8 hours.  
Adults: 250-500 mg. every 6 hours. See accompanying literature.

Manufactured by Beecham Laboratories,  
Div. of Beecham Inc., Bristol, Tenn. 37620

Distributed by  
**AYERST LABORATORIES INCORPORATED**  
NEW YORK, N.Y. 10017

\* Mfr. lic'd. under © 705-484.

6526B

Made in U.S.A.

Note: No refrigeration required before mixing. After mixing, suspension may be kept at room temperature for 7 days or in a refrigerator for 14 days without significant loss of potency.

**SHAKE WELL BEFORE USING • KEEP TIGHTLY CLOSED**

Control No. \_\_\_\_\_

Exp. Date \_\_\_\_\_

(Tear along dotted line.)

Directions for mixing: Add 66 cc. of water and shake vigorously. Each 5 cc. (one teaspoonful) will then contain 250 mg. of ampicillin in a pleasant cherry-flavored suspension.

5 Gm.  
Ampicillin  
100 cc.  
(When  
mixed)

When reconstituted,  
each 5 cc. contains  
**250 mg.**  
ampicillin as  
the trihydrate.

**Ayerst**

CAUTION: Federal law  
prohibits dispensing  
without prescription.

**PENBRITIN**  
(AMPICILLIN)  
for  
**ORAL SUSPENSION**

Usual Dosage—  
Children: 50-100 mg./kg./day in divided doses every 6-8 hours.  
Adults: 250-500 mg. every 6 hours. See accompanying literature.

Manufactured by Beecham Laboratories,  
Div. of Beecham Inc., Bristol, Tenn. 37620

Distributed by  
**AYERST LABORATORIES INCORPORATED**  
NEW YORK, N.Y. 10017

\*Mfr. Reg. under © 705,484.

6350C

Made in U.S.A.

**Note:** No refrigeration required before mixing. After mixing, suspension may be kept at room temperature for 7 days or in a refrigerator for 14 days without significant loss of potency.

**SHAKE WELL BEFORE USING • KEEP TIGHTLY CLOSED**

Control No.

Exp. Date

(Tear along dotted line.)

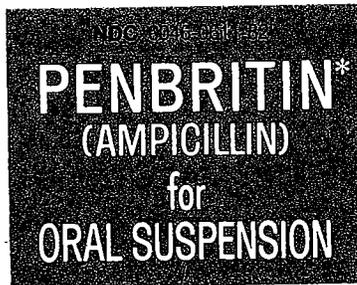
**Directions for mixing:** Add 132 cc. of water and shake vigorously. Each 5 cc. (one teaspoonful) will then contain 250 mg. of ampicillin in a pleasant cherry-flavored suspension.

**Ayerst**

10 Gm.  
Ampicillin  
200 cc.  
(When  
mixed)

When reconstituted,  
each 5 cc. contains  
**250 mg.**  
ampicillin as  
the trihydrate.

CAUTION: Federal law  
prohibits dispensing  
without prescription.



**Usual dosage—**  
Children: 50-100 mg./kg./day in divided doses every 6-8 hours.  
Adults: 250-500 mg. every 6 hours. See accompanying literature.

Manufactured by Beecham Laboratories,  
Div. of Beecham Inc., Bristol, Tenn. 37620

Distributed by  
**AYERST LABORATORIES INCORPORATED**  
NEW YORK, N.Y. 10017

Made in U.S.A.

6527B

\*Mfr. lic'd. under © 705,484.

# PENBRITIN\*

(ampicillin)

for  
**ORAL SUSPENSION**  
 125 mg./5 cc.  
 and  
 250 mg./5 cc.

**PEDIATRIC DROPS**  
 for  
**ORAL SUSPENSION**  
 100 mg./cc.

**CAUTION:** Federal law prohibits dispensing without prescription.

## DESCRIPTION

Chemical name: D(-)-alpha-aminobenzyl penicillin

PENBRITIN is an orally active, semisynthetic broad spectrum penicillin. It is inactivated by penicillinase.

## ACTIONS

### Microbiologic:

Ampicillin appears to act primarily by interfering with the synthesis or maintenance of the bacterial cell wall. It strongly inhibits the early lag and logarithmic phases of bacterial multiplication. In *in vitro* studies, ampicillin is bactericidal.

PENBRITIN is effective against the usual penicillin-susceptible gram-positive organisms, and in addition, many gram-negative pathogens. It is active *in vitro* against many strains of the following bacteria:

**GRAM-POSITIVE** — Alpha and beta hemolytic streptococci, nonpenicillinase-producing staphylococci, *Diplococcus pneumoniae*, *Clostridia* species, *Bacillus anthracis*, most strains of enterococci.

**GRAM-NEGATIVE** — *Haemophilus influenzae*, *Neisseria gonorrhoeae* and meningitidis, *Proteus mirabilis*, *Escherichia coli*, *Salmonella* (including *S. typhosa*), *Neisseria catarrhalis*, *Bacteroides funduliformis*, and *Shigella*.

All strains of *Pseudomonas* and most strains of *Klebsiella-Aerobacter* are resistant. Because ampicillin is destroyed by penicillinase, PENBRITIN is not effective against penicillinase-producing bacteria.

### Pharmacologic:

PENBRITIN is stable in acid and is therefore not destroyed by gastric juice. (Food, however, retards absorption.) PENBRITIN is well absorbed and produces high and persistent blood levels of unbound ampicillin. Ampicillin is the least protein bound of all the penicillins, averaging 20 percent as contrasted with 60 to 90 percent for the others. Blood serum levels of approximately 2 mcg./ml. are achieved within one to two hours following a 250 mg. oral dose to fasting adults. Detectable amounts persist in the blood for about six hours. There are high concentrations in the bile and urine. Ampicillin diffuses readily into most body tissues and fluids. However, penetration into the cerebral spinal fluid occurs only with meningeal inflammation. Ampicillin is excreted in the urine, largely unchanged, and this excretion can be delayed by concurrent administration of probenecid.

## INDICATIONS

PENBRITIN is indicated in the treatment of infections due to susceptible strains of the following:

**GRAM-NEGATIVE** organisms: *Shigella*, *Salmonella* (including *S. typhosa*), *H. influenzae*, *E. coli*, *P. mirabilis*, *N. gonorrhoeae*, and *N. meningitidis*.

**GRAM-POSITIVE** organisms: Streptococci, nonpenicillinase-producing staphylococci, and *D. pneumoniae*.

Bacteriologic studies to determine the causative organisms and their sensitivity to ampicillin should be performed. Because PENBRITIN is a broad spectrum antibiotic, therapy may be instituted prior to the results of sensitivity testing.

## CONTRAINDICATIONS

PENBRITIN is contraindicated in patients with a history of hypersensitivity to any penicillin.

## WARNINGS

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL THERAPY, IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. THESE REACTIONS ARE MORE APT TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR HYPERSENSITIVITY REACTIONS TO MULTIPLE ALLERGENS.

THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE THERAPY WITH A PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, AND OTHER ALLERGENS.

IF AN ALLERGIC REACTION OCCURS, THE DRUG SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE, OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

USAGE IN PREGNANCY: Safety for use in pregnancy has not been established.

## PRECAUTIONS

As with any antibiotic preparation, constant observation for signs of overgrowth of nonsusceptible organisms, including fungi, is essential. Should superinfection occur (usually involving *Aerobacter*, *Pseudomonas*, or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.

Periodic assessment of renal, hepatic, and hematopoietic function should be made during prolonged therapy. This is particularly important in prematures, neonates and other infants.

## ADVERSE REACTIONS

As with other penicillins, it may be expected that untoward reactions will be essentially limited to sensitivity phenomena. These are more likely to occur in individuals with a history of allergy, asthma, hay fever, or urticaria.

The following adverse reactions have been reported as associated with the use of ampicillin:

Gastrointestinal — glossitis, stomatitis, black "hairy" tongue, nausea, vomiting, diarrhea. (These reactions are usually associated with oral administration.)

# PENBRITIN (ampicillin) for Oral Suspension & Pediatric Drops for Oral Suspension cont'd.

Hypersensitivity reactions — erythematous maculopapular rashes have been reported fairly frequently; urticaria, erythema multiforme, and an occasional case of exfoliative dermatitis have been reported. Anaphylaxis is usually associated with parenteral administration.

*Note:* Urticaria, other skin rashes, and serum sickness-like reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, ampicillin should be discontinued unless, in the opinion of the physician, the condition being treated is life-threatening and amenable only to ampicillin therapy.

Hepatic — A moderate rise in serum glutamic oxaloacetic transaminase (SGOT) has been noted, particularly in infants. The significance of this finding is unknown.

Hemic and lymphatic — anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia, and agranulocytosis have been reported. These are usually reversible on discontinuation of the drug, and are believed to be hypersensitivity phenomena.

## DOSAGE AND ADMINISTRATION

Infection	Usual Dosage* Adults	Usual Dosage* Children†
Respiratory tract	250 mg. q. 6 h.	50 mg./kg./day in equal doses q. 6-8 h.
Gastrointestinal tract	500 mg. q. 6 h.	100 mg./kg./day in equal doses q. 6-8 h.
Genitourinary tract		
Urethritis in Males or Females due to <i>N. gonorrhoeae</i>	3.5 Gm. single oral dose administered simultaneously with 1.0 Gm. of probenecid  In the treatment of complications of gonorrheal urethritis, such as prostatitis and epididymitis, prolonged and intensive therapy is recommended.  Cases of gonorrhea with a suspected primary lesion of syphilis should have dark-field examinations before receiving treatment. In all other cases where concomitant syphilis is suspected, monthly serologic tests should be made for a minimum of four months.	

\*Larger than usual dosages may be required for stubborn or severe infections. Smaller doses than those recommended above should not be used.

†The children's dosage is intended for individuals whose weight will not cause a dosage to be calculated greater than that recommended for adults. Children weighing more than 20 kg. (44 lb.) should be given the adult recommended dosage.

## PEDIATRIC DROPS:

A suggested dosage regimen is:

Under 12 lb. — 0.6 cc. q. 6 hours.

12-25 lb. — 1.0 cc. q. 6 hours.

25-44 lb. — 2.0 cc. q. 6 hours.

**DURATION OF TREATMENT:** Medications should be continued for at least 48 to 72 hours after all symptoms have subsided or cultures have become negative. For any infection caused by hemolytic streptococci, at least 10 days of treatment is recommended to help prevent the occurrence of acute rheumatic fever or glomerulonephritis.

## DIRECTIONS FOR MIXING ORAL SUSPENSIONS

Prepare suspensions at time of dispensing as follows: Add the required amount of water (see table below) to the bottle and shake vigorously. Each teaspoonful (5 cc.) of reconstituted Oral Suspension will contain 125 mg. or 250 mg. ampicillin, depending upon the initial concentration. Each cc. of reconstituted Pediatric Drops will contain 100 mg. ampicillin.

Bottle Size	Amount of Water Required for Reconstitution
100 cc. Oral Suspension	66 cc.
200 cc. Oral Suspension	132 cc.
20 cc. Pediatric Drops	11.5 cc.

SHAKE WELL BEFORE USING.

## STABILITY

**ORAL SUSPENSION:** No refrigeration required before mixing. After mixing, suspension may be kept at room temperature (70° F.) for 7 days or in a refrigerator (40° F.) for 14 days without significant loss of potency. KEEP TIGHTLY CLOSED.

**PEDIATRIC DROPS:** No refrigeration required before mixing. After mixing, suspension may be kept in a refrigerator for 14 days without significant loss of potency. KEEP TIGHTLY CLOSED.

## HOW SUPPLIED

**PENBRITIN (ampicillin) for Oral Suspension — when reconstituted:**

Each 5 cc. (one teaspoonful) contains 125 mg. ampicillin as the trihydrate. Bottles for 100 cc. (NDC 0046-0607-86) and 200 cc. (NDC 0046-0607-82).

Each 5 cc. (one teaspoonful) contains 250 mg. ampicillin as the trihydrate. Bottles for 100 cc. (NDC 0046-0611-86) and 200 cc. (NDC 0046-0611-82).

**PENBRITIN (ampicillin) PEDIATRIC DROPS for Oral Suspension — when reconstituted:**

Each cc. contains 100 mg. ampicillin as the trihydrate. Bottles for 20 cc. (NDC 0046-0625-20).

Distributed by  
**AYERST LABORATORIES INCORPORATED**  
New York, N.Y. 10017

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**Approval Package for:**

**APPLICATION NUMBER:**

**60-666 supplement**

Trade Name: Pen A for Oral Suspension  
125mg/5mL and 250mg/5mL

Generic Name: ampicillin trihydrate

Sponsor: Beecham Laboratories

Approval Date: January 20, 1976

# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:**

**60-666 supplement**

## CONTENTS

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Bioequivalence Review(s)	
Administrative Document(s)	
Correspondence	

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**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**APPROVAL LETTER**

①

A-6  
Powers

# Beecham laboratories

65 INDUSTRIAL SOUTH, CLIFTON, NEW JERSEY 07012

201-778-9000

REGULATORY DEPARTMENT

CABLE ADDRESS "BEECHPRÖD"  
TELEX 133471

*ok to sign out  
JOP 1/20/76*

January 16, 1976

Food and Drug Administration  
Certifiable Drug Review Staff (HFD-535) No.  
Division of Generic Drug Monographs  
Bureau of Drugs  
5600 Fishers Lane  
Rockville, Maryland 20852

For the Department of Health, Education and Welfare  
Food and Drug Administration  
Washington, D.C.  
1/20/76  
*[Signature]*

Re: #60-666 (440.107c)

Gentlemen:

Reference is made to Beecham Laboratories' approved Form 6 #60-666 covering Ampicillin for Oral Suspension, distributed by Pfizer Inc. under the trade name Pen A.

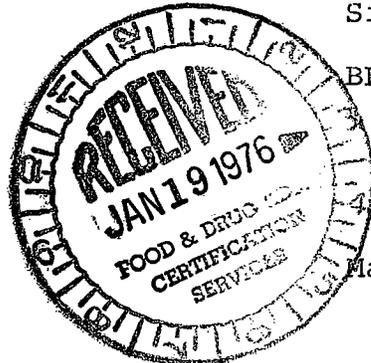
We are submitting, in triplicate, final printed labeling which was revised to reflect the Pfipharmecs Division signature and NDC number and the addition of the manufacturer's identification.

Sincerely,

BEECHAM LABORATORIES

*G. Vadnai*

George Vadnai  
Manager, Governmental Affairs



GSV:dmm  
Enclosures

02379

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

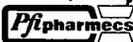
**60-666 supplement**

**FINAL PRINTED LABELING**

NDC 0995-0311-44 2394

**Pen A<sup>®</sup>**  
ampicillin  
**FOR ORAL  
SUSPENSION**  
**125 mg/5 ml<sup>†</sup>**  
**100 ml**  
equivalent to  
2.5 g ampicillin

CAUTION: Federal law prohibits  
dispensing without prescription.

Distributed by  
 **Pf** **pharmecs** DIVISION  
PFIZER INC., NEW YORK, N.Y. 10017

**READ ACCOMPANYING PROFESSIONAL INFORMATION**  
**USUAL DOSAGE**—Children: 50 to 100 mg/kg/day in divided  
doses every 6 to 8 hours.  
Adults: 250 to 500 mg every 6 hours.  
Manufactured by Beecham Laboratories, Div. Beecham Inc., Bristol,  
TN 37620 from Pfizer's bulk penicillin G. 9022/c

**RECOMMENDED STORAGE IN DRY FORM**

STORE BELOW 86° F. (30° C.)  
When reconstituted as directed each 5 ml (1 teaspoonful)  
contains ampicillin trihydrate equivalent to 125 mg ampicillin.  
Directions for reconstitution: Add 66 ml of water. For ease  
of preparation, tap gently, add water in 2 portions.  
Shake well after each addition.  
MADE IN U.S.A. I

EXP.

LOT NO.

**KEEP CONTAINER TIGHTLY CLOSED—SHAKE WELL BEFORE USING**  
When suspension is stored at room temperature discard  
unused portion after 7 days; when stored under  
refrigeration discard unused portion after 14 days.

NDC 0995-0311-91 2395

# Pen A<sup>®</sup>

ampicillin

FOR ORAL  
SUSPENSION

125 mg/5 ml<sup>†</sup>

200 ml

equivalent to  
5.0 g ampicillin

CAUTION: Federal law prohibits  
dispensing without prescription.

Distributed by



PFIZER INC., NEW YORK, N.Y. 10017

**RECOMMENDED STORAGE IN DRY FORM**

STORE BELOW 86° F. (30° C.)

(When reconstituted as directed each 5 ml (1 teaspoonful) contains ampicillin trihydrate equivalent to 125 mg ampicillin.)

Directions for reconstitution: Add 132 ml of water. For ease of preparation, tap gently, add water in 2 portions. Shake well after each addition.

MADE IN U.S.A. 1

EXP.

LOT NO.

**KEEP CONTAINER TIGHTLY CLOSED - SHAKE WELL BEFORE USING**

When suspension is stored at room temperature discard unused portion after 7 days; when stored under refrigeration discard unused portion after 14 days.

**READ ACCOMPANYING PROFESSIONAL INFORMATION**

**USUAL DOSAGE**

Children: 50 to 100 mg/kg/day in divided doses every 6 to 8 hours.

Adults: 250 to 500 mg every 6 hours.

Manufactured by Beecham Laboratories, Div. Beecham Inc., Bristol, TN 37620 from Pfizer's bulk penicillin G.

9016/C

NDC 0995-0312-44 2396

# Pen A<sup>®</sup>

ampicillin

## FOR ORAL SUSPENSION

### 250 mg/5 ml

100 ml  
equivalent to  
5.0 g ampicillin

CAUTION: Federal law prohibits  
dispensing without prescription.

Distributed by  
 DIVISION  
PFIZER INC., NEW YORK, N.Y. 10017

**RECOMMENDED STORAGE: IN DRY FORM.**

STORE BELOW 86° F. (30° C.)  
When reconstituted as directed each 5 ml (1 teaspoonful) contains ampicillin trihydrate equivalent to 250 mg ampicillin.  
Directions for reconstitution: Add 68 ml of water. For ease of preparation, tap gently and water in 2 portions. For ease, shake well after each addition.  
MADE IN U.S.A. 1

Exp.

LOT NO.

**KEEP CONTAINER TIGHTLY CLOSED-SHAKE WELL BEFORE USING**  
When suspension is stored at room temperature discard unused portion after 7 days. When stored under refrigeration discard unused portion after 14 days.

**READ ACCOMPANYING PROFESSIONAL INFORMATION**  
**USUAL DOSAGE:** Children: 50 to 100 mg/kg/day in divided doses every 6 to 8 hours.  
Adults: 250 to 500 mg every 6 hours.  
Manufactured by Beecham Laboratories, Div. Beecham Inc., Bristol, TN 37620 from Pfizer's bulk penicillin G. 8019/c

NDC 0995-0312-91 2397

# Pen A<sup>®</sup> ampicillin

FOR ORAL  
SUSPENSION

**250 mg/5 ml**

**200 ml**

equivalent to  
10.0 g ampicillin

CAUTION: Federal law prohibits  
dispensing without prescription.

Distributed by



PFIZER INC., NEW YORK, N.Y. 10017

**RECOMMENDED STORAGE: IN DRY FORM  
STORE BELOW 86° F. (30° C.)**  
When reconstituted as directed each 5 ml (1 teaspoonful)  
contains ampicillin trihydrate equivalent to 250 mg ampicillin.  
Directions for reconstitution: Add 192 ml of water. For ease  
of preparation, tap gently; add water in 2 portions.  
Shake well after each addition.

MADE IN U.S.A.

EXP.

LOT NO.

**KEEP CONTAINER TIGHTLY CLOSED - SHAKE WELL BEFORE USING**  
When suspension is stored at room temperature discard  
unused portion after 7 days; when stored under  
refrigeration discard unused portion after 14 days.

READ ACCOMPANYING PROFESSIONAL INFORMATION

USUAL DOSAGE

Children: 50 to 100 mg/kg/day in divided doses every 6 to 8 hours.

Adults: 250 to 500 mg every 6 hours.

Manufactured by Beecham Laboratories, Inc., Bala Cynwyd, Pa.  
Product No. 37620. © 1978 Beecham Laboratories, Inc.

9019/C



# Pen A<sup>®</sup>

## ampicillin



CAPSULES  
250 mg  
and  
500 mg

for  
ORAL SUSPENSION  
125 mg/5 ml  
and  
250 mg/5 ml

### Description

Pen A (ampicillin) is derived from the penicillin nucleus, 6-amino-penicillanic acid (6-APA). Chemically it is D (-)  $\alpha$ -aminobenzyl penicillin.

### Actions

#### MICROBIOLOGY:

Pen A (ampicillin) is similar to benzyl penicillin in its bactericidal action against sensitive organisms during the stage of active multiplication. It acts through the inhibition of biosynthesis of cell wall mucopeptide. Pen A (ampicillin) differs in *in vitro* spectrum from benzyl penicillin in the gram-negative spectrum. It exerts high *in vitro* activity against many strains of *Hemophilus influenzae*, *Neisseria gonorrhoeae*, *Neisseria meningitidis* and *Neisseria catarrhalis*, *Escherichia coli*, *Proteus mirabilis*, *Bacteroides funduliformis*, *Salmonellae* and *Shigellae*.

*In vitro* studies have also demonstrated the sensitivity of many strains of the following gram-positive bacteria: alpha- and beta-hemolytic streptococci, *Diplococcus pneumoniae*, nonpenicillinase-producing staphylococci, *Bacillus anthracis*, and most strains of enterococci and clostridia. Ampicillin generally provides less *in vitro* activity than penicillin G against gram-positive bacteria. Because it does not resist destruction by penicillinase, it is not effective against penicillinase-producing bacteria, particularly resistant staphylococci. All strains of *Pseudomonas* and most strains of *Klebsiella* and *Aerobacter* are resistant.

#### PHARMACOLOGY:

Pen A (ampicillin) is acid stable and therefore well absorbed. Food, however, retards absorption. Blood serum levels of approximately 2 mcg/ml are attained within 1-2 hours following a 250 mg oral dose given to fasting adults. Detectable amounts persist for about 6 hours. Pen A (ampicillin) diffuses readily into all body tissues and fluids with the exception of brain and spinal fluid except when meninges are inflamed. Higher serum levels are obtained following I.M. injection. Most of the ampicillin is excreted unchanged in the urine and this excretion can be delayed by concurrent administration of probenecid. The active form appears in the bile in higher concentrations than found in the serum. Pen A (ampicillin) is the least serum bound of all the penicillins, averaging about 20% compared to approximately 60%-90% for other penicillins.

### Indications

Pen A (ampicillin) is indicated in the treatment of infections due to susceptible strains of the following:

*gram-negative organisms*—*Shigellae*, *Salmonellae* (including *S. typhosa*), *H. influenzae*, *E. coli* and *P. mirabilis*, *N. gonorrhoeae*, and *N. meningitidis*;  
*gram-positive organisms*—Streptococci, *D. pneumoniae*, and nonpenicillinase-producing staphylococci.

Because of its wide spectrum and bactericidal action, it may be useful in instituting therapy; however, bacteriological studies to determine the causative organisms and their sensitivity to ampicillin should be performed.

Indicated surgical procedures should be performed.

### Contraindications

The use of this drug is contraindicated in individuals with a history of an allergic reaction to any of the penicillins.

### Warnings

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL THERAPY, IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. THESE REACTIONS ARE MORE APT TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR HYPERSENSITIVITY REACTIONS TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE THERAPY WITH A PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, THE DRUG SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED.

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE, OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

### USAGE IN PREGNANCY:

Safety for use in pregnancy has not been established.

### Precautions

As with any antibiotic preparation, constant observations for signs of overgrowth of nonsusceptible organisms, including fungi, are essential. Should superinfection occur (usually involving *Aerobacter*, *Pseudomonas*, or *Candida*), the drug should be discontinued and/or appropriate therapy instituted. As with

### Precautions (continued)

any potent agent, it is advisable to check periodically for organ system dysfunction during prolonged therapy; this includes renal, hepatic, and hematopoietic systems. This is particularly important in prematures, neonates and other infants.

### Adverse Reactions

As with other penicillins, it may be expected that untoward reactions will be essentially limited to sensitivity phenomena. They are more likely to occur in individuals who have previously demonstrated hypersensitivity to penicillins and in those with a history of allergy, asthma, hay fever, or urticaria. The following adverse reactions have been reported as associated with the use of ampicillin:

**Gastrointestinal**—glossitis, stomatitis, black "hairy" tongue, nausea, vomiting, and diarrhea. (These reactions are usually associated with oral dosage forms.)

**Hypersensitivity reactions**—An erythematous maculopapular rash has been reported fairly frequently. Urticaria and erythema multiforme have been reported occasionally. A few cases of exfoliative dermatitis have been reported. Anaphylaxis is the most serious reaction experienced and has usually been associated with the parenteral dosage form.

**Note:** Urticaria, other skin rashes, and serum sickness-like reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, ampicillin should be discontinued, unless, in the opinion of the physician, the condition being treated is life-threatening and amenable only to ampicillin therapy.

**Liver**—A moderate rise in serum glutamic oxaloacetic transaminase (SGOT) has been noted, particularly in infants, but the significance of this finding is unknown.

**Hemic and Lymphatic Systems**—Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia, and agranulocytosis have been reported during therapy with the penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be sensitivity reactions.

### Dosage

**Infections of the ear, nose, throat, and lower respiratory tract** due to streptococci, pneumococci, and nonpenicillinase-producing staphylococci, and also those infections of the upper and lower respiratory tract due to *H. influenzae*:

Adults— 250 mg every 6 hours.

Children— 50 mg/kg/day in divided doses every 6 or 8 hours.

**Infections of the genitourinary tract caused by sensitive gram-negative and gram-positive bacteria:**

Adults— 500 mg every 6 hours. Larger doses may be required for severe infections.

Children— 100 mg/kg/day in divided doses every 6 hours.

**Uncomplicated urethritis due to *N. gonorrhoeae*:**

Adult males and females—3.5 grams single oral dose administered simultaneously with 1.0 gram of probenecid.

**Cases of gonorrhea with a suspected lesion of syphilis should have dark field examinations before receiving ampicillin, and monthly serological tests for a minimum of 4 months.**

**Infections of the gastrointestinal tract:**

Adults— 500 mg every 6 hours.

Children— 100 mg/kg/day in divided doses every 6 hours.

Larger doses may be required for stubborn or severe infections. The children's dosage is intended for individuals whose weight will not cause a dosage to be calculated greater than that recommended for adults. Children weighing more than 20 kg should be dosed according to the adult recommendations.

It should be recognized that in the treatment of chronic urinary tract and intestinal infections, frequent bacteriological and clinical appraisals are necessary. Smaller doses than those recommended above should not be used. Even higher doses may be needed at times. In stubborn infections, therapy may be required for several weeks. It may be necessary to continue clinical and/or bacteriological follow-up for several months after cessation of therapy.

Treatment should be continued for a minimum of 48 to 72 hours beyond the time that the patient becomes asymptomatic or evidence of bacterial eradication has been obtained. It is recommended that there be at least 10 days' treatment for any infection caused by hemolytic streptococci, to help prevent the occurrence of acute rheumatic fever or glomerulonephritis.

### Directions for Mixing Oral Suspension

Prepare suspension at time of dispensing as follows: Add 66 ml of water to the 100 ml package and 132 ml of water to the 200 ml package. Shake vigorously. This will provide 100 and 200 ml of suspension, respectively. Each teaspoonful (5 ml) will contain 125 mg or 250 mg ampicillin. SHAKE WELL BEFORE USING. Keep bottle tightly closed. The reconstituted suspension is stable for 7 days at room temperature (70° F.) or 14 days under refrigeration (40° F.).

### How Supplied

Pen A (ampicillin) Capsules: Ampicillin trihydrate equivalent to 250 mg or 500 mg ampicillin per capsule.

250 mg: bottles of 100, 500, and unit dose (10 x 10's).

500 mg: bottles of 100, and unit dose (10 x 10's).

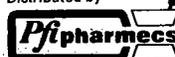
Pen A (ampicillin) for Oral Suspension: Each 5 ml of reconstituted suspension contains ampicillin trihydrate equivalent to 125 mg or 250 mg ampicillin.

125 mg/5 ml: bottles of 100 ml and 200 ml.

250 mg/5 ml: bottles of 100 ml and 200 ml.

Manufactured by Beecham Laboratories,  
Div. Beecham Inc., Bristol, TN 37620  
from Pfizer's bulk penicillin G.

Distributed by

 **Pfizer** DIVISION  
PFIZER INC., NEW YORK, N.Y. 10017

60-2373-00-1  
9049/D

Printed in U.S.A.  
Revised Jan. 1976

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**Approval Package for:**

**APPLICATION NUMBER:**

**60-666 supplement**

Generic Name: Ampicillin Trihydrate for Oral  
Suspension 125mg/5mL and  
250mg/5mL

Sponsor: Beecham Laboratories

Approval Date: March 5, 1976

# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:**

**60-666 supplement**

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**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**APPROVAL LETTER**

Harrison

# Beecham laboratories

65 INDUSTRIAL SOUTH, CLIFTON, NEW JERSEY 07012 201-778-9000

REGULATORY DEPARTMENT

CABLE ADDRESS "BEECHPROD"  
TELEX 133471

March 2, 1976

Date Approved 3/5/76

Food and Drug Administration  
Bureau of Drugs  
Div. of Generic Drug Monographs  
Certifiable Drug Review Staff (HFD-535)  
5600 Fishers Lane  
Rockville, Maryland 20852

Account No. \_\_\_\_\_

Signed John L. Harrison  
For the Commissioner of Food and Drugs  
Department of Health, Education and  
Welfare

Re: # 60-666 (440.107c)

Gentlemen:

Reference is made to Beecham Laboratories' approved Form 6 antibiotic application for Ampicillin for Oral Suspension. We hereby wish to supplement our Application to provide for a revised formula for the 125 mg/ 5 ml dosage strength. The new formula is identical to the previous one, except \_\_\_\_\_ is utilized to replace the recently banned \_\_\_\_\_

This supplement is submitted in triplicate.

Sincerely,

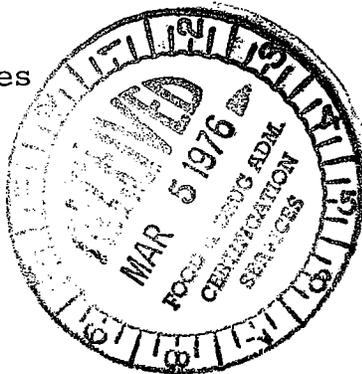
BEECHAM LABORATORIES

*George Vadnai*

George Vadnai  
Manager,  
Governmental Affairs

GSV:sc  
Enclosures

60173



**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**Approval Package for:**

**APPLICATION NUMBER:**

**60-666 supplement**

Trade Names: Totacillin, Alpen, Penbritin, and  
Pen A for Oral Suspension  
125mg/5mL and 250mg/5mL

Generic Name: ampicillin trihydrate

Sponsor: Beecham Laboratories

Approval Date: May 12, 1976

# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:**

**60-666 supplement**

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Correspondence	X

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**CENTER FOR DRUG  
EVALUATION AND  
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**APPLICATION NUMBER:**

**60-666 supplement**

**APPROVAL LETTER**

**Beecham**  
laboratories

65 INDUSTRIAL SOUTH, CLIFTON, NEW JERSEY 07012

201-778-9000

REGULATORY DEPARTMENT

CABLE ADDRESS "BEECHPROD"  
TELEX 133471

March 19, 1976

Date Approved 5/12/76

Food and Drug Administration  
Certification Drug Review Staff (HFD-535)  
Division of Generic Drug Monographs  
Bureau of Drugs  
5600 Fishers Lane  
Rockville, Maryland 20852

Account No. \_\_\_\_\_

Signed Wm D. Johnson

For The Commissioner of Food and Drug  
Department of Health, Education and  
Welfare

Re: #60-666 (440.107c)

Gentlemen:

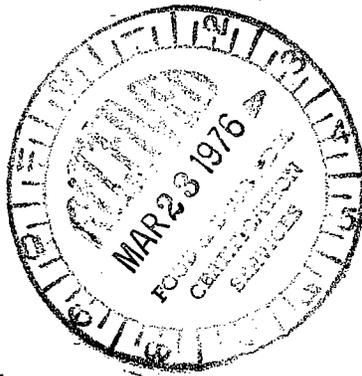
Reference is made to Beecham Laboratories' approved Form 6 Antibiotic Application for Ampicillin Trihydrate for Oral Suspension 125 mg/5 ml and 250 mg/5 ml, distributed under the trade names of Totacillin, Alpen, Penbritin and Pen A. We hereby wish to supplement our Application to provide additional data and request the extension of the expiry date to 48 months.

Under separate cover, the following samples are being transmitted:

5 bottles 125 mg/5 ml	Lot #498
5 bottles 125 mg/5 ml	Lot #499
5 bottles 250 mg/5 ml	Lot #500
5 bottles 250 mg/5 ml	Lot #501

This supplement is transmitted in triplicate.

03557



Sincerely,

BEECHAM LABORATORIES

*George Vadnai*

George Vadnai  
Manager, Governmental Affairs

GSV:dmm  
Enclosures

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**ADMINISTRATIVE  
DOCUMENT(S)**

**Redacted** 4

**Page(s) of trade**

**secret and /or**

**confidential**

**commercial**

**information**

Beecham acct no 576



DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
ROCKVILLE, MARYLAND 20852

May 11, 1976

Our Reference: Trade Letter Number 22

NOTICE OF INCREASE IN ANTIBIOTIC CERTIFICATION FEES

PLEASE TAKE NOTICE that the Food and Drug Administration has increased the chargeable fees for Certification Services for each batch of antibiotic drugs submitted.

To keep as your ready reference, we have attached a new list showing the numeric code for the type of tests performed, together with the revised schedule of chargeable fees. This should enable you to check the tests performed and the charges shown on the bills as they arrive at your office.

The fee schedule is officially published in the Code of Federal Regulations, Title 21 Section 431.53 Fees. (revised: effective as of May 3, 1976).

A handwritten signature in cursive script, which appears to read "Robert L. Sorensen", is written over the typed name.

Robert L. Sorensen  
Certification Services Branch (HFD-332)

Attachment: Schedule of Fees

**Redacted** 4

**Page(s) of trade**

**secret and /or**

**confidential**

**commercial**

**information**

MEMO RECORD

AVOID ERRORS  
PUT IT IN WRITING

DATE  
MARCH 25, 1976

FROM: MILTON EISLER HFD-535

OFFICE

TO: BERNARD ARRET HFD-431

DIVISION OF GENERIC  
DRUG MONOGRAPHS

SUBJECT: BECKMAN LABORATORIES - AMPICILLIN

SUMMARY  
TRIHYDRATE FOR ORAL SUSPENSION, 125 mg/5ml  
+ 250 mg/5ml. - REQUEST EXTENSION OF  
EXPIRATION DATE TO 48 MONTHS -

The firm has submitted extensive data including potency (Chemical, Hydroxylamine), microbiological potency, pH & moisture.

They have submitted samples from aged bottles (-x 125mg/5ml + -x 250mg/5ml)

Please test all batches for comparison with all monograph specifications. If possible check volumes following reconstitution.

The potency determinations should include:  
a) potency following reconstitution  
b) " " " + storage (R.T.) for 7 days  
c) " " " (refrigerated) " 14 days

Enclosed  
1) samples  
2) submission March 19, 1976

SIGNATURE

Milton

DOCUMENT NUMBER

60-666(440.107c)

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**CORRESPONDENCE**



DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE  
 PUBLIC HEALTH SERVICE  
 FOOD AND DRUG ADMINISTRATION  
 ROCKVILLE, MARYLAND 20852

Our Reference: 60-666 (440.107c) Date: May 12, 1976

LETTER OF APPROVAL--	RE: <u>Your Batchmark No.</u>	<u>FDA</u>	<u>No.</u>
<u>Extension Of Expiration Date</u>	498) 125 mg/5ml.	S3119	
Your Request Dated: 3/9/76	499)	S3120	
	500) 250 mg/5ml.	S3121	
	501)	S3122	

Mr. George Vadnai  
 Beecham Laboratories  
 Clifton, New Jersey 07012

Dear Mr. Vadnai:

Our laboratories have completed testing samples from the above-referenced aged batches. On the basis of the data available to us at this time we believe your proposal to extend the expiration date on future batches of the referenced product has been adequately substantiated.

BEECHAM LABORATORIES is hereby authorized to use an expiration date of 48 months on all new batches of Ampicillin Trihydrate For Oral Suspension, (Detail generic name, potency[ies], type packaging.) 125 mg./5ml. and 250 mg./5ml. submitted for certification testing after the date of this letter, whose manufacture, packaging and labeling is in agreement with the procedures, specifications, and labeling described in the approved FDA Form 6. An approved copy of your request for the new dating period is enclosed for your records.

The fees charged for conducting the confirmatory tests and assays in our laboratories are indicated on the enclosed copies of FDA Form 1687. Your antibiotic certification account number 576 will be billed in the usual manner for such tests performed in the amount of \$ 456.00.

Sincerely,

Milton Eisler  
 Consumer Safety Officer  
 Certifiable Drug Review Staff (HFD-535)  
 Division of Generic Drug Monographs

cc: NWR-Bo

HFD-535

HFD-535/OD

HFD-430/lab

Fee Clerk

K. Whitley HFD-332

Pugliese HFV-200

slr:hb

Enclosures

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**Approval Package for:**

**APPLICATION NUMBER:**

**60-666 supplement**

Trade Name: Pen A for Oral Suspension  
125mg/5mL and 250mg/5mL

Generic Name: ampicillin trihydrate

Sponsor: Pfizer

Approval Date: May 20, 1976

# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:**

**60-666 supplement**

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**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**APPROVAL LETTER**

Date Approved 5/20/76  
Account No. \_\_\_\_\_  
Signed John D. Harrison  
For the Commissioner of Food and Drugs  
Food and Drug Administration



A-6  
~~1.) Harrison~~  
~~2.) Eister~~

PHARMACEUTICALS

PFIZER INC., 235 E. 42ND ST., NEW YORK, N.Y. 10017

May 11, 1976

Mr. John D. Harrison  
Certifiable Drug Review Staff (HFD-535)  
Office of Scientific Evaluation  
Bureau of Drugs  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20852

look for  
number

RE: Pen-A Powder (ampicillin trihydrate) For Oral Suspension  
Section 440.197c (60-666)

Dear Mr. Harrison:

We are herewith submitting stability data including potency and \_\_\_\_\_ results for the subject product stored in packages with child-resistant closures for up to 12 months.

Please add this information to the file for Pen-A Powder (ampicillin trihydrate) For Oral Suspension, Section 440.197c (60-666).

Sincerely,

Harry M. Kaufman  
Associate Director  
Drug Regulatory Affairs Division  
PFIZER PHARMACEUTICALS



HMK/sp  
Enclosure

CONFIDENTIAL

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**Approval Package for:**

**APPLICATION NUMBER:**

**60-666 supplement**

Trade Name: Penbritin for Oral Suspension  
125mg/5mL and 250mg/5mL

Generic Name: ampicillin trihydrate

Sponsor: Beecham Laboratories

Approval Date: May 20, 1976

# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:**

**60-666 supplement**

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Microbiology Review(s)	
Bioequivalence Review(s)	
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Correspondence	

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**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**APPROVAL LETTER**

**Beecham**  
laboratories

65 INDUSTRIAL SOUTH, CLIFTON, NEW JERSEY 07012

201-778-9000

REGULATORY DEPARTMENT

CABLE ADDRESS "BEECHPROD"  
TELEX 133471

May 18, 1976

*apt. signout  
GVP 5/20/76*

A-6  
~~XXXXXX~~

Food and Drug Administration  
Certifiable Drug Review Staff (HFD-535)  
Division of Generic Drug Monographs  
Bureau of Drugs  
5600 Fishers Lane  
Rockville, Maryland 20852

For use of 7500 and 7500 Administrative  
6/20/76  
for the Department of Health, Education and Welfare  
Department of Health, Education and Welfare

Re: #60-666 (440.107c)

Gentlemen:

Reference is made to Beecham Laboratories' approved Form 6 Anti-biotic Application #60-666 covering Ampicillin for Oral Suspension, distributed by Ayerst Laboratories Inc. under the trade name Penbritin.

We are hereby submitting, in triplicate, final printed labeling revised to reflect the use of metric abbreviations (ml); the package insert also reflects the inclusion of "21.1°C" as the equivalent of 70°F and "4.4°C" as the equivalent of 40°F in the Storage/Stability recommendations.



Sincerely,

BEECHAM LABORATORIES

*G. Vadnai*

George Vadnai  
Manager, Governmental Affairs

GSV:dmm  
Enclosures

4439

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**FINAL PRINTED LABELING**

Note: No refrigeration required before mixing. After mixing, the suspension may be kept at room temperature for 7 days or in a refrigerator for 14 days without significant loss of potency.

**SHAKE WELL BEFORE USING • KEEP TIGHTLY CLOSED**

Control No. \_\_\_\_\_  
Exp. Date \_\_\_\_\_  
(Tear along dotted line.)  
Directions for mixing: Tap bottle gently to loosen powder. Add 100 ml of water. Shake well after preparation. Each 5 ml (1 teaspoonful) of reconstituted suspension contains 125 mg of ampicillin in a pleasant cherry-flavored suspension.

**PENBRITIN\***  
(AMPICILLIN)  
for  
**ORAL SUSPENSION**

2.5 g  
Ampicillin  
100 ml  
(When  
mixed)

When reconstituted,  
each 5 ml contains  
**125 mg**  
ampicillin as  
the trihydrate.



CAUTION: Federal law prohibits dispensing without prescription.

Usual dosage—  
Children: 50-100 mg /kg /day in divided doses every 6-8 hours.  
Adults: 250-500 mg every 6 hours. See accompanying literature.

Manufactured by Beecham Laboratories,  
Div. of Beecham Inc., Bristol, Tenn. 37620

Distributed by  
**AYERST LABORATORIES, INCORPORATED**  
NEW YORK, N.Y. 10017

\*Nfr. lic. # under © 705,484. 6349D Made in U.S.A.

Note: No refrigeration required before mixing. After mixing, suspension may be kept at room temperature for 7 days or in a refrigerator for 14 days without significant loss of potency.

**SHAKE WELL BEFORE USING • KEEP TIGHTLY CLOSED**

Control No.

Exp. Date

(Tear along dotted line.)

Directions for mixing: Tap bottle gently to loosen powder for ease of preparation. Add a total of 132 ml of water in 2 portions—shake well after each addition of water. When reconstituted, each 5 ml (1 teaspoonful) contains 125 mg of ampicillin in pleasant cherry-flavored suspension.

**PENBRITIN\***  
(AMPICILLIN)  
for  
**ORAL SUSPENSION**

5 g  
Ampicillin  
200 ml  
(When  
mixed)

When reconstituted,  
each 5 ml contains  
**125 mg**  
ampicillin as  
the trihydrate.

**Ayerst.**

CAUTION: Federal law  
prohibits dispensing  
without prescription.

Usual dosage—  
Children: 50-100 mg./kg./day in divided doses every 6-8 hours.  
Adults: 250-500 mg. every 6 hours. See accompanying literature.

Manufactured by Beecham Laboratories,  
Div. of Beecham Inc., Bristol, Tenn. 37620

Distributed by  
**AYERST LABORATORIES INCORPORATED**  
NEW YORK, N.Y. 10017

Made in U.S.A.

6526C

\* Mfr. lic'd. under © 705,484.

Note: No refrigeration required before mixing. After mixing, suspension must be stored in a refrigerator for 7 days or in a refrigerator for 14 days without significant loss of potency.

**SHAKE WELL BEFORE USING • KEEP TIGHTLY CLOSED**

Control No.

Exp. Date

(Tear along dotted line.)  
Directions for mixing: Tap bottle gently to loosen powder for ease of preparation. Add a total of 66 ml of water in 2 portions—shake well after each addition. Each 5 ml (1 teaspoonful) contains 250 mg of ampicillin in a pleasant cherry flavored suspension.

**5 g  
Ampicillin  
100 ml  
(When  
mixed)**

When reconstituted,  
each 5 ml contains  
**250 mg**  
ampicillin as  
the trihydrate.

**Ayerst**

CAUTION: Federal law  
prohibits dispensing  
without prescription.

**PENBRITIN**  
(AMPICILLIN)  
for  
**ORAL SUSPENSION**

Usual dosage—  
Children: 50-100 mg/kg/day, in divided doses every 6-8 hours.  
Adults: 250-500 mg every 6 hours. See accompanying literature.

Manufactured by Beecham Laboratories,  
Div. of Beecham Inc., Bristol, Tenn. 37620

Distributed by  
**AYERST LABORATORIES INCORPORATED**  
NEW YORK, N.Y. 10017

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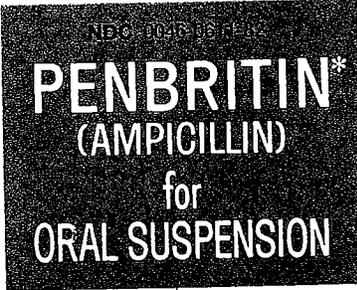
Note: No refrigeration required before mixing. After mixing, suspension must be kept at room temperature for 7 days or in a refrigerator for 14 days without significant loss of potency.

**SHAKE WELL BEFORE USING • KEEP TIGHTLY CLOSED**

Control No.

Exp. Date (Tear along dotted line.)

Directions for mixing: Tap bottle gently to loosen powder for ease of preparation. Add a total of 132 ml of water in 2 portions—shake well after each addition of water. When reconstituted, each 5 ml (1 teaspoonful) contains 250 mg of ampicillin in a pleasant cherry-flavored suspension.



10 g  
Ampicillin  
200 ml  
(When  
mixed)

When reconstituted,  
each 5 ml contains

**250 mg**  
ampicillin as  
the trihydrate.

**Ayerst.**

CAUTION: Federal law  
prohibits dispensing  
without prescription.

Usual dosage—  
Children: 50-100 mg /kg /day in divided doses every 6-8 hours.  
Adults: 250-500 mg every 6 hours. See accompanying literature.

Manufactured by Beecham Laboratories,  
Div. of Beecham Inc., Bristol, Tenn. 37620

Distributed by  
**AYERST LABORATORIES INCORPORATED**  
NEW YORK, N.Y. 10017

Made in U.S.A.

6527C

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# PENBRITIN\*

(ampicillin)

for  
**ORAL SUSPENSION**  
 125 mg/5 ml  
 and  
 250 mg/5 ml

**PEDIATRIC DROPS**  
 for  
**ORAL SUSPENSION**  
 100 mg/ml

**CAUTION:** Federal law prohibits dispensing without prescription.

## DESCRIPTION

Chemical name: D(—)-alpha-aminobenzyl penicillin

PENBRITIN is an orally active, semisynthetic broad spectrum penicillin. It is inactivated by penicillinase.

## ACTIONS

### Microbiologic:

Ampicillin appears to act primarily by interfering with the synthesis or maintenance of the bacterial cell wall. It strongly inhibits the early lag and logarithmic phases of bacterial multiplication. *In vitro* studies, ampicillin is bactericidal.

PENBRITIN is effective against the usual penicillin-susceptible gram-positive organisms, and in addition, many gram-negative pathogens. It is active *in vitro* against many strains of the following bacteria:

**GRAM-POSITIVE** — Alpha and beta hemolytic streptococci, nonpenicillinase-producing staphylococci, *Diplococcus pneumoniae*, *Clostridia* species, *Bacillus anthracis*, most strains of enterococci.

**GRAM-NEGATIVE** — *Haemophilus influenzae*, *Neisseria gonorrhoeae* and *meningitidis*, *Proteus mirabilis*, *Escherichia coli*, *Salmonella* (including *S. typhosa*), *Neisseria catarrhalis*, *Bacteroides funduliformis*, and *Shigella*.

All strains of *Pseudomonas* and most strains of *Klebsiella-Aerobacter* are resistant. Because ampicillin is destroyed by penicillinase, PENBRITIN is not effective against penicillinase-producing bacteria.

### Pharmacologic:

PENBRITIN is stable in acid and is therefore not destroyed by gastric juice. (Food, however, retards absorption.) PENBRITIN is well absorbed and produces high and persistent blood levels of unbound ampicillin. Ampicillin is the least protein bound of all the penicillins, averaging 20 percent as contrasted with 60 to 90 percent for the others. Blood serum levels of approximately 2 mcg/ml are achieved within one to two hours following a 250 mg oral dose to fasting adults. Detectable amounts persist in the blood for about six hours. There are high concentrations in the bile and urine. Ampicillin diffuses readily into most body tissues and fluids. However, penetration into the cerebral spinal fluid occurs only with meningeal inflammation. Ampicillin is excreted in the urine, largely unchanged, and this excretion can be delayed by concurrent administration of probenecid.

## INDICATIONS

PENBRITIN is indicated in the treatment of infections due to susceptible strains of the following:

**GRAM-NEGATIVE organisms:** *Shigella*, *Salmonella* (including *S. typhosa*), *H. influenzae*, *E. coli*, *P. mirabilis*, *N. gonorrhoeae*, and *N. meningitidis*.

**GRAM-POSITIVE organisms:** Streptococci, nonpenicillinase-producing staphylococci, and *D. pneumoniae*.

Bacteriologic studies to determine the causative organisms and their sensitivity to ampicillin should be performed. Because PENBRITIN is a broad spectrum antibiotic, therapy may be instituted prior to the results of sensitivity testing.

## CONTRAINDICATIONS

PENBRITIN is contraindicated in patients with a history of hypersensitivity to any penicillin.

## WARNINGS

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL THERAPY, IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. THESE REACTIONS ARE MORE APT TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR HYPERSENSITIVITY REACTIONS TO MULTIPLE ALLERGENS.

THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE THERAPY WITH A PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, AND OTHER ALLERGENS.

IF AN ALLERGIC REACTION OCCURS, THE DRUG SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE, OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

USAGE IN PREGNANCY: Safety for use in pregnancy has not been established.

## PRECAUTIONS

As with any antibiotic preparation, constant observation for signs of overgrowth of nonsusceptible organisms, including fungi, is essential. Should superinfection occur (usually involving *Aerobacter*, *Pseudomonas*, or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.

Periodic assessment of renal, hepatic, and hematopoietic function should be made during prolonged therapy. This is particularly important in prematures, neonates and other infants.

## ADVERSE REACTIONS

As with other penicillins, it may be expected that untoward reactions will be essentially limited to sensitivity phenomena. These are more likely to occur in individuals with a history of allergy, asthma, hay fever, or urticaria.

The following adverse reactions have been reported as associated with the use of ampicillin:

Gastrointestinal — glossitis, stomatitis, black "hairy" tongue, nausea, vomiting, diarrhea. (These reactions are usually associated with oral administration.)

## PENBRITIN (ampicillin) for Oral Suspension & Pediatric Drops for Oral Suspension cont'd.

Hypersensitivity reactions — erythematous maculopapular rashes have been reported fairly frequently; urticaria, erythema multiforme, and an occasional case of exfoliative dermatitis have been reported. Anaphylaxis is usually associated with parenteral administration.

Note: Urticaria, other skin rashes, and serum sickness-like reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, ampicillin should be discontinued unless, in the opinion of the physician, the condition being treated is life-threatening and amenable only to ampicillin therapy.

Hepatic — A moderate rise in serum glutamic oxaloacetic transaminase (SGOT) has been noted, particularly in infants. The significance of this finding is unknown.

Hemic and lymphatic — anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia, and agranulocytosis have been reported. These are usually reversible on discontinuation of the drug, and are believed to be hypersensitivity phenomena.

### DOSAGE AND ADMINISTRATION

Infection	Usual Dosage* Adults	Usual Dosage* Children†
Respiratory tract	250 mg q. 6 hours	50 mg/kg/day in equal doses q. 6-8 hours
Gastrointestinal tract Genitourinary tract	500 mg q. 6 hours	100 mg/kg/day in equal doses q. 6-8 hours
Urethritis in Males or Females due to <i>N. gonorrhoeae</i>	3.5 g single oral dose administered simultaneously with 1.0 g of probenecid	

In the treatment of complications of gonorrheal urethritis, such as prostatitis and epididymitis, prolonged and intensive therapy is recommended.

Cases of gonorrhea with a suspected primary lesion of syphilis should have dark-field examinations before receiving treatment. In all other cases where concomitant syphilis is suspected, monthly serologic tests should be made for a minimum of four months.

\*Larger than usual dosages may be required for stubborn or severe infections. Smaller doses than those recommended above should not be used.

†The children's dosage is intended for individuals whose weight will not cause a dosage to be calculated greater than that recommended for adults. Children weighing more than 20 kg (44 lb) should be given the adult recommended dosage.

### PEDIATRIC DROPS:

A suggested dosage regimen is:

Under 12 lb — 0.6 ml q. 6 hours  
12-25 lb — 1.0 ml q. 6 hours  
25-44 lb — 2.0 ml q. 6 hours

DURATION OF TREATMENT: Medications should be continued for at least 48 to 72 hours after all symptoms have subsided or cultures have become negative. For any infection caused by hemolytic streptococci, at least 10 days of treatment is recommended to help prevent the occurrence of acute rheumatic fever or glomerulonephritis.

### DIRECTIONS FOR MIXING ORAL SUSPENSIONS

Prepare suspensions at time of dispensing as follows: Add the required amount of water (see table below) to the bottle and shake vigorously. Each teaspoonful (5 ml) of reconstituted Oral Suspension will contain 125 mg or 250 mg ampicillin, depending upon the initial concentration. Each ml of reconstituted Pediatric Drops will contain 100 mg ampicillin.

Bottle Size	Amount of Water Required for Reconstitution
100 ml Oral Suspension	66 ml
200 ml Oral Suspension	132 ml
20 ml Pediatric Drops	11.5 ml

SHAKE WELL BEFORE USING.

### STABILITY

ORAL SUSPENSION: No refrigeration required before mixing. After mixing, suspension may be kept at room temperature [21.3° C (70° F)] for 7 days or in a refrigerator [4.4° C (40° F)] for 14 days without significant loss of potency. KEEP TIGHTLY CLOSED.

PEDIATRIC DROPS: No refrigeration required before mixing. After mixing, suspension may be kept in a refrigerator for 14 days without significant loss of potency. KEEP TIGHTLY CLOSED.

### HOW SUPPLIED

PENBRITIN (ampicillin) for Oral Suspension — when reconstituted:

Each 5 ml (one teaspoonful) contains 125 mg ampicillin as the trihydrate. Bottles for 100 ml (NDC 0046-0607-86) and 200 ml (NDC 0046-0607-82).

Each 5 ml (one teaspoonful) contains 250 mg ampicillin as the trihydrate. Bottles for 100 ml (NDC 0046-0611-86) and 200 ml (NDC 0046-0611-82).

PENBRITIN (ampicillin) PEDIATRIC DROPS for Oral Suspension — when reconstituted:

Each ml contains 100 mg ampicillin as the trihydrate. Bottles for 20 ml (NDC 0046-0625-20).

Distributed by  
**AYERST LABORATORIES INCORPORATED**  
New York, N.Y. 10017

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**Approval Package for:**

**APPLICATION NUMBER:**

**60-666 supplement**

Trade Name: Pen A for Oral Suspension  
125mg/5mL and 250mg/5mL

Generic Name: ampicillin trihydrate

Sponsor: Pfizer

Approval Date: July 21, 1976

# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:**

**60-666 supplement**

## CONTENTS

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Reviews / Information Included in this ANDA Review.

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EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**APPROVAL LETTER**

①

H-6  
~~POWER~~



PHARMACEUTICALS

PFIZER INC., 235 E. 42ND ST., NEW YORK, N.Y. 10017

*Acto sign out  
JDB 7/21/76*

July 15, 1976

Mr. John D. Harrison  
Certifiable Drug Review Staff (HFD-535)  
Bureau of Drugs  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20852

(For use of Food and Drug Administration)	
Date approved	7/21/76
Signed	<i>[Signature]</i>
For the Commissioner of Food and Drugs Food and Drug Administration Department of Health, Education, and Welfare	

RE: Pen-A (ampicillin) For Oral Suspension  
440.107c (60-666)

Dear Mr. Harrison:

As Mr. J. P. Aterno discussed with you late last month, the Skaggs Drug Company has asked us to apply "Distributed by Skaggs" stickers on several lots of antibiotic products which they have purchased from Pfizer. We will place these stickers on each immediate container (and on each individual folding carton, where applicable) in such a manner that no label copy will be obscured.

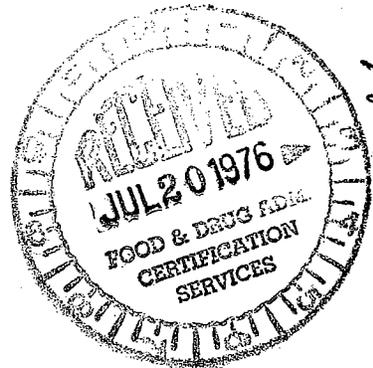
Accordingly, for the subject product, enclosed please find a sample of the Skaggs sticker.

Please add this information to the file for Pen-A (ampicillin) For Oral Suspension, 440.107c (60-666). Thank you very much.

Sincerely yours,

*David C. Oppenheimer*

David C. Oppenheimer  
Associate Director  
Drug Regulatory Affairs Division  
PFIZER PHARMACEUTICALS



DCO/smh  
Enclosure

05207

**CONFIDENTIAL**

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EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**FINAL PRINTED LABELING**

Distributed by **SKAGGS**

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**Approval Package for:**

**APPLICATION NUMBER:**

**60-666 supplement**

Generic Name: Ampicillin Trihydrate for Oral  
Suspension 125mg/5mL and  
250mg/5mL

Sponsor: Beecham Laboratories

Approval Date: October 8, 1976

# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:**

**60-666 supplement**

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EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**APPROVAL LETTER**

H-6  
Harrison

# Beecham laboratories

65 INDUSTRIAL SOUTH, CLIFTON, NEW JERSEY 07012

201-778-9000

REGULATORY DEPARTMENT

CABLE ADDRESS "BEECHPROD"  
TELEX 133471

October 5, 1976

Food and Drug Administration  
Certifiable Drug Review Staff (HFD-535)  
Division of Generic Drug Monographs  
Bureau of Drugs  
5600 Fishers Lane  
Rockville, Maryland 20852

Date Rec'd 10/8/76  
Approved

Signed *John D. Curran*  
For the Director  
Dose #60-666 (440.107c)

Gentlemen:

Reference is made to Beecham Laboratories' approved Form 6 Antibiotic Application #60-666 covering Ampicillin for Oral Suspension. In compliance with the Federal Register notice of September 23, 1976 we are hereby supplementing our Application to provide for the replacement of \_\_\_\_\_ with \_\_\_\_\_. The appropriate revised manufacturing procedures are enclosed. The first \_\_\_\_\_ production lots will be placed into our stability testing program and the results will be periodically reported.

This supplement is submitted in triplicate.

Sincerely,

BEECHAM LABORATORIES

*George Vadnai*

George Vadnai  
Manager, Governmental Affairs



GSV:sc  
Enclosures

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**Approval Package for:**

**APPLICATION NUMBER:**

**60-666 supplement**

Trade Name: Penbritin for Oral Suspension  
125mg/5mL and 150mg/5mL

Generic Name: ampicillin trihydrate

Sponsor: Beecham-Massengill Pharmaceuticals

Approval Date: November 11, 1974

# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:**

**60-666 supplement**

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Microbiology Review(s)	
Bioequivalence Review(s)	
Administrative Document(s)	
Correspondence	X

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RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**APPROVAL LETTER**

*A/C*

# Beecham-Massengill Pharmaceuticals

DIVISION OF BEECHAM INC. CLIFTON, NEW JERSEY



65 INDUSTRIAL SOUTH  
CLIFTON, NEW JERSEY 07012  
REGULATORY DEPARTMENT

CABLE ADDRESS "BEECHPROD"  
TELEX 133471

PHONE: 201-778-9000

October 31, 1974

Date Approved 11/11/74  
Account No. \_\_\_\_\_

Mr. John D. Harrison  
Certifiable Drug Review Staff (HFD-145)  
Div. of Anti-Infective Drug Products  
Food and Drug Administration  
Bureau of Drugs  
5600 Fishers Lane  
Rockville, Maryland 20852

Signed John D. Harrison  
For the Commissioner of the Food and Drugs  
Department of Health, Education and  
Welfare

Re: #50-019  
#60-680 (440.107c)

Dear Mr. Harrison:

In compliance with your letter of October 8, 1974, concerning Penbritin (ampicillin) Pediatric Drops for Oral Suspension, we hereby submit, in triplicate, the appropriate manufacturing and control data for the above product, which reflects the change from the            ampicillin to the ampicillin trihydrate formula.

The information contained in this submission is to be considered confidential.

Sincerely,

BEECHAM-MASSENGILL PHARMACEUTICALS

*G. Vadnai*

George Vadnai  
Manager, Governmental Affairs

GSV:dmm  
Enclosures

cc: Mr. E. Hiross (Ayerst)

RECEIVED  
NOV 13 1974

G. YADNAI

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RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**CORRESPONDENCE**



DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
ROCKVILLE, MARYLAND 20857  
September 28, 1977

Our reference:

60-680

60-666

George Vadnai  
Manager, Governmental Affairs  
Beecham Laboratories  
Clifton, New Jersey 07012

Dear Sir:

Due to recent adverse reaction reports published in the medical literature and reported to the Food and Drug Administration by at least one Ampicillin oral dosage form manufacturer, our medical staff finds it necessary to request a revision in the package insert(s) for these drugs. The revision is in the "Gastrointestinal" sub-section of the "Adverse Reactions" section. Please revise this sub-section by adding the following two adverse reactions:

1. enterocolitis
2. pseudomembranous colitis.

The above two adverse reactions should be printed between the word "vomiting" and the word "and" in the presently approved "Gastrointestinal" sub-section.

Twelve copies of a revised package insert in final printed form should be submitted within 180 days of the date of this letter.

Sincerely yours,

I. David Powers  
Certifiable Drug Review Staff (HFD-535)  
Division of Generic Drug Monographs

cc:

~~HFD-535~~

HFD-535/OD

HFD-430/lab.

IDPowers:hb

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**Approval Package for:**

**APPLICATION NUMBER:**

**60-666 supplement**

Trade Name: Penbritin for Oral Suspension  
125mg/5mL and 250mg/5mL

Generic Name: ampicillin trihydrate

Sponsor: Beecham Laboratories

Approval Date: February 14, 1977

# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:**

**60-666 supplement**

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**APPLICATION NUMBER:**

**60-666 supplement**

**APPROVAL LETTER**

**Beecham**  
laboratories

*OK to sign out  
WEM  
2-14-77*

*[Handwritten signature]*

65 INDUSTRIAL SOUTH, CLIFTON, NEW JERSEY 07012

201-778-9000

REGULATORY DEPARTMENT

CABLE ADDRESS "BEECHPROD"  
TELEX 133471

February 7, 1977

Date Approved 2/14/77

Account No. \_\_\_\_\_

Food and Drug Administration  
Certifiable Drug Review Staff (HFD-535)  
Division of Generic Drug Monographs  
Bureau of Drugs  
5600 Fishers Lane  
Rockville, Maryland 20852

Signed *[Signature]*  
For the Commissioner of Food and Drug  
Department of Health, Education and  
Welfare

Re: #60-666 (440.107c)

Gentlemen:

In accordance with my discussion with Mr. W. Magner on February 4, 1977, we hereby supplement our Form 6 Antibiotic Application for Ampicillin Trihydrate for Oral Suspension to include Penbritin (ampicillin) Pediatric Drops for Oral Suspension, 100 mg/ml, distributed by Ayerst Laboratories as an additional dosage size under this Form 6 number (#60-666).

As the enclosed cover letter indicates, this supplement was originally filed under Form 6 #60-680 on October 31, 1974 and was approved on November 11, 1974.

This supplement is submitted in triplicate.

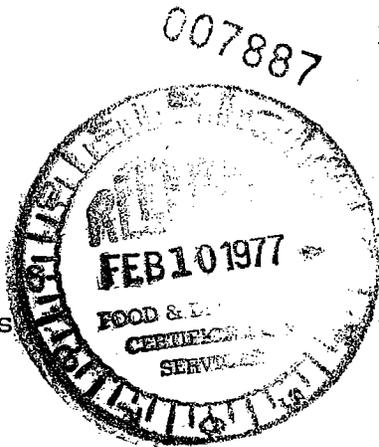
Sincerely,

BEECHAM LABORATORIES

*George Vadnai*

George Vadnai  
Manager, Governmental Affairs

GSV:dmm  
Enclosures



**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**Approval Package for:**

**APPLICATION NUMBER:**

**60-666 supplement**

Trade Names: Totacillin, Alpen, Penbritin, and Pen  
A for Oral Suspension 125mg/5mL  
and 250mg/5mL

Generic Name: ampicillin trihydrate

Sponsor: Beecham Laboratories

Approval Date: November 4, 1977

# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:**

**60-666 supplement**

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### Reviews / Information Included in this ANDA Review.

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Chemistry Review(s)	
Microbiology Review(s)	
Bioequivalence Review(s)	
Administrative Document(s)	X
Correspondence	X

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RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**APPROVAL LETTER**

**Beecham**  
laboratories

65 INDUSTRIAL SOUTH, CLIFTON, NEW JERSEY 07012

201-778-9000

REGULATORY DEPARTMENT

CABLE ADDRESS "BEECHPROD"  
TELEX 133471

*OK  
M.E.  
11/4/77  
Eisler*

**Date Approved** 11/4/77

**Account No.** \_\_\_\_\_

Food and Drug Administration  
Certifiable Drug Review Staff (HFD-535)  
Division of Generic Drug Monographs  
Bureau of Drugs  
5600 Fishers Lane  
Rockville, Maryland 20857

**Signed** *[Signature]*  
For The Commissioner of Food and Drugs  
Department of Health, Education and  
Welfare

Re: #60-666 (440.107c)

Gentlemen:

Reference is made to Beecham Laboratories' approved Form 6 Antibiotic Application for Ampicillin Trihydrate for Oral Suspension 125 mg/5 ml and 250 mg/5 ml, distributed under the trade names of Totacillin, Alpen, Penbritin and Pen A. We hereby wish to supplement our Application to provide additional stability data and request the extension of the expiry date to 60 months.

Under separate cover, the following samples are being transmitted:

5 bottles 125mg/5 ml	Lot #498 - 53501
5 bottles 125mg/5 ml	Lot #499 53502
5 bottles 250mg/5 ml	Lot #500 53503
5 bottles 250mg/5 ml	Lot #502 53504

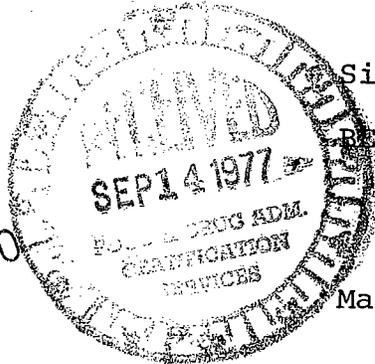
This supplement is transmitted in triplicate.

Sincerely,

BEECHAM LABORATORIES

*G. Vadnai*

George Vadnai  
Manager, Governmental Affairs



010730

GSV:dmm  
Enclosures

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**ADMINISTRATIVE  
DOCUMENT(S)**

NOTICE OF APPROVAL  
NEW DRUG APPLICATION OR SUPPLEMENT

ANDA NUMBER  
**FORM 6-# 60-666**  
DATE APPROVAL LETTER ISSUED  
**11/4/77**

TO:  
Press Relations Staff (HFI-40)

FROM:  
 Bureau of Drugs  
 Bureau of Veterinary Medicine

ATTENTION  
Forward original of this form for publication only after approval letter has been issued and the date of approval has been entered above.

TYPE OF APPLICATION

ORIGINAL NDA  SUPPLEMENT TO **FORM 6**  
 ABBREVIATED ORIGINAL NDA  SUPPLEMENT TO ANDA

CATEGORY  
 HUMAN  VETERINARY

TRADE NAME (or other designated name) AND ESTABLISHED OR NONPROPRIETARY NAME (if any) OF DRUG  
**TOTACILLIN, ALPEN, PENBRITIN + PEN A; AMPICILLIN TRIHYDRATE FOR O.S.**

DOSAGE FORM  
**POWDER FOR ORAL SUSPENSION**

HOW DISPENSED  
 RX  OTC

ACTIVE INGREDIENT(S) (as declared on label. List by established or nonproprietary name(s) and include amount(s), if amount is declared on label.)  
**AMPICILLIN TRIHYDRATE  
125mg/sml  
250mg/sml**

APPEARS THIS WAY  
ON ORIGINAL

NAME OF APPLICANT (Include City and State)

**BEECHAM LABORATORIES  
CLIFTON, NEW JERSEY**

PRINCIPAL INDICATION OR PHARMACOLOGICAL CATEGORY

**ANTIBACTERIAL (ANTI-INFECTIVE)**

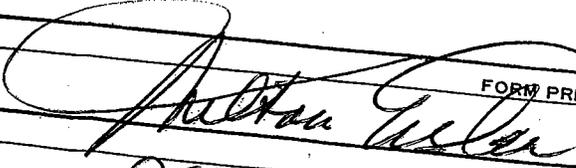
ANIMAL SPECIES FOR WHICH APPROVED

COMPLETE FOR VETERINARY ONLY

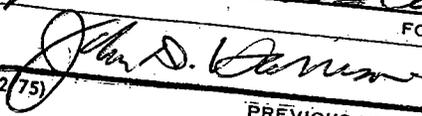
CHANGE APPROVED TO PROVIDE FOR

COMPLETE FOR SUPPLEMENT ONLY

**EXTENSION OF EXPIRATION DATE**

NAME  FORM PREPARED BY

DATE **Nov. 4, 1977**

NAME  FORM APPROVED BY

DATE **Nov. 4, 1977**

DRM FD 1642 (2/75)

PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

**Redacted** 4

**Page(s) of trade**

**secret and /or**

**confidential**

**commercial**

**information**

# MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION

TO : M. Eisler - HFD-535

DATE: Nov. 1, 1977

FROM : B. Arret, Deputy Director, NCAA  
HFD-431

SUBJECT: EXTENSION OF EXPIRATION DATE; BEECHAM TRIHYDRATE FOR  
ORAL SUSPENSION, BEECHAM LABS (60-666)

The 125 mg/5 ml and 250 mg/5 ml sizes were assayed at the time of reconstitution, after seven days storage at room temperature and 14 days storage in the refrigerator. The potencies at reconstitution are all above 100% of label and there is no significant loss in potency when stored at either temperature.

The original assays when these batches were manufactured are not available in our files.

*B. Arret*  
B. Arret

cc:  
HFD-400  
HFD-401  
HFD-430/31  
HFD-436 (2)

BArret:bhp

DATE  
SEPT. 16, 1977

FROM: MILTON EISLER AFD-535

OFFICE  
DIVISION OF GENERIC  
DRUG MONOGRAPHS

TO: DR. PETER WEISS AFD-430

SUBJECT: BEECHAM LABS - ~~AMOX~~ AMPICILLIN

SUMMARY: TRIHYDRATE FOR ORAL SUSPENSION,  
125mg/5ml + 250mg/5ml - REQUEST  
EXTENSION OF EXPIRATION DATE TO SIXTY (60)  
MONTHS

The firm has provided considerable <sup>data</sup> for  
a number of aged batches as well as samples  
from -- (9) aged batches -- x 125mg/5ml;  
-- x 250mg/5ml

- Please have labs test all aged batches for  
stability following request
- ① " " " " R. Temp Storage - 7 days
  - ② " " " " Refrigerated " - 14 days
  - ③ " " " " " " " " " " " "

④ those additional tests you consider necessary  
and/or desirable

Unlabeled  
① Submission date (received) Sept 14, 1977

- ② Samples

53501  
2  
3  
4

SIGNATURE  
*Milton Eisler*

DOCUMENT NUMBER  
60-666-(440.107c)



**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**CORRESPONDENCE**



DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE  
 PUBLIC HEALTH SERVICE  
 FOOD AND DRUG ADMINISTRATION  
 ROCKVILLE, MARYLAND 20852

Our Reference: 60-666 (440.107c) Date: November 4, 1977

LETTER OF APPROVAL--  
Extension Of Expiration Date  
 Your Request Dated:  
 9/12/77

RE: <u>Your Batchmark No.</u>	<u>FDA No.</u>
498)	S3501
499) 125 mg./5ml.	S3502
500) 250 mg./5ml.	S3503
502)	S3504

George Vadnai  
 Manager, Governmental Affairs  
 Beecham Laboratories  
 Clifton, New Jersey 07012

Dear Mr. Vadnai:

Our laboratories have completed testing samples from the above-referenced aged batches. On the basis of the data available to us at this time we believe your proposal to extend the expiration date on future batches of the referenced product has been adequately substantiated.

BEECHAM LABORATORIES is hereby authorized to use an expiration date of 60 months on all new batches of AMPICILLIN TRIHYDRATE FOR ORAL SUSPENSION, (Detail generic name, potency[ies], type packaging.) 125 mg/5ml. and 250 mg/5ml.

submitted for certification testing after the date of this letter, whose manufacture, packaging and labeling is in agreement with the procedures, specifications, and labeling described in the approved FDA Form 6. An approved copy of your request for the new dating period is enclosed for your records.

The fees charged for conducting the confirmatory tests and assays in our laboratories are indicated on the enclosed copies of FDA Form 1687. Your antibiotic certification account number 576 will be billed in the usual manner for such tests performed in the amount of \$ 456.00.

Sincerely,

cc: NWK-DO  
 HFD-535  
 HFD-535/OD  
 HFD-430/lab.  
 HFD-332/KWhitley  
 HFD-332/Fee Clerk  
 HFV-234/FPugliese  
 MEisler:hb

Milton Eisler  
 Consumer Safety Officer  
 Certifiable Drug Review Staff (HFD-535)  
 Division of Generic Drug Monographs

Enclosures

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**Approval Package for:**

**APPLICATION NUMBER:**

**60-666 supplement**

Trade Names: Totacillin for Oral Suspension  
125mg/5mL and 250mg/5mL

Generic Name: ampicillin trihydrate

Sponsor: Beecham Laboratories

Approval Date: November 17, 1977

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**CONTENTS**

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**Reviews / Information Included in this ANDA Review.**

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Approval Letter(s)	X
Tentative Approval Letter(s)	
Final Printed Labeling	X
CSO Labeling Review(s)	
Medical Officer Review(s)	
Chemistry Review(s)	
Microbiology Review(s)	
Bioequivalence Review(s)	
Administrative Document(s)	
Correspondence	

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**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**APPROVAL LETTER**

*Powers*

# Beecham laboratories

65 INDUSTRIAL SOUTH, CLIFTON, NEW JERSEY 07012 201-778-9000

REGULATORY DEPARTMENT

**(For use of Food and Drug Administration)**

*ok to sign out  
11/17/77*

CABLE ADDRESS "BEECHPROD"  
TELEX 133471

Date approved 11/17/77

Approved by [Signature] November 14, 1977

Signed [Signature]

For the Commissioner of Food and Drugs  
Food and Drug Administration

Department of Health, Education, and Welfare

Food and Drug Administration  
Certifiable Drug Review Staff (HFD-535)  
Division of Generic Drug Monographs  
Bureau of Drugs  
5600 Fishers Lane  
Rockville, Maryland 20857

Re: #60-666 (440.107c)

Gentlemen:

Reference is made to Beecham Laboratories' approved Form 6 Antibiotic Application for Ampicillin Trihydrate for Oral Suspension 125 mg/5 ml and 250 mg/5 ml. We hereby wish to supplement our Application to provide for twelve copies of the final printed package insert which was revised in accordance with Mr. I. David Powers' letter of September 28, 1977.

This supplement is transmitted in triplicate.

Sincerely,

BEECHAM LABORATORIES

*George Vadnai*

George Vadnai  
Manager, Governmental Affairs



GSV:dmm  
Enclosures

000559

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**FINAL PRINTED LABELING**

# TOTACILLIN®

## ampicillin

CAPSULES  
250 mg  
and  
500 mg

for  
ORAL SUSPENSION  
125 mg/5 ml  
and  
250 mg/5 ml

### DESCRIPTION

TOTACILLIN (Ampicillin) is derived from the penicillin nucleus, 6-aminopenicillanic acid (6-APA), isolated by Beecham. Chemically it is D (-)  $\alpha$ -aminobenzyl penicillin trihydrate.

### ACTIONS

#### MICROBIOLOGY:

TOTACILLIN (Ampicillin) is similar to benzyl penicillin in its bactericidal action against sensitive organisms during the stage of active multiplication. It acts through the inhibition of biosynthesis of cell wall mucopeptide. TOTACILLIN (Ampicillin) differs in *in vitro* spectrum from benzyl penicillin in the Gram-negative spectrum. It exerts high *in vitro* activity against many strains of *Haemophilus influenzae*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Neisseria catarrhalis*, *Escherichia coli*, *Proteus mirabilis*, *Bacteroides funduliformis*, *Salmonellae* and *Shigellae*.

*In vitro* studies have also demonstrated the sensitivity of many strains of the following Gram-positive bacteria: alpha- and beta-hemolytic streptococci, *Diplococcus pneumoniae*, nonpenicillinase-producing staphylococci, *Bacillus anthracis*, and most strains of enterococci and clostridia. Ampicillin generally provides less *in vitro* activity than penicillin G against Gram-positive bacteria. Because it does not resist destruction by penicillinase, it is not effective against penicillinase-producing bacteria, particularly resistant staphylococci. All strains of *Pseudomonas* and most strains of *Klebsiella* and *Aerobacter* are resistant.

#### PHARMACOLOGY:

TOTACILLIN (Ampicillin) is acid stable and, therefore, well absorbed. Food, however, retards absorption. Blood serum levels of approximately 2 mcg/ml are attained within 1-2 hours following a 250 mg oral dose given to fasting adults. Detectable amounts persist for about 6 hours.

TOTACILLIN (Ampicillin) diffuses readily into all body tissues and fluids with the exception of brain and spinal fluid except when meninges are inflamed. Higher serum levels are obtained following I.M. injection. Most of the Ampicillin is excreted unchanged in the urine and this excretion can be delayed by concurrent administration of probenecid. The active form appears in the bile in higher concentrations than found in the serum. TOTACILLIN (Ampicillin) is one of the least serum bound of all the penicillins averaging about 20% compared to approximately 60%-90% for other penicillins.

### INDICATIONS

TOTACILLIN (Ampicillin) is indicated in the treatment of infections due to susceptible strains of the following:

Gram-negative Organisms: *Shigellae*, *Salmonellae* (including *S. typhosa*), *H. influenzae*, *E. coli*, *P. mirabilis*, *N. gonorrhoeae*, and *N. meningitidis*.

Gram-positive Organisms: Streptococci, *D. pneumoniae*, and nonpenicillinase-producing staphylococci.

Because of its wide spectrum and bactericidal action, it may be useful in instituting therapy; however, bacteriological studies to determine the causative organisms and their sensitivity to Ampicillin should be performed. Indicated surgical procedures should be performed.

### CONTRAINDICATIONS

A history of allergic reaction to any of the penicillins is a contraindication.

### WARNINGS

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL THERAPY, IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. THESE REACTIONS ARE MORE APT TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR HYPERSENSITIVITY REACTIONS TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE THERAPY WITH A PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, THE DRUG SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE, OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

#### USAGE IN PREGNANCY:

Safety for use in pregnancy has not been established.

### PRECAUTIONS

As with any antibiotic preparation, constant observation for signs of overgrowth of nonsusceptible organisms, including fungi, is essential. Should superinfection occur (usually involving *Aerobacter*, *Pseudomonas*, or *Candida*), the drug should be discontinued and/or appropriate therapy instituted. As with any potent agent, it is advisable to check periodically for organ system dysfunction.

As with other penicillins, it may be expected that untoward reactions will be essentially limited to sensitivity phenomena. They are more likely to occur in individuals who have previously demonstrated hypersensitivity to penicillins and in those with a history of allergy, asthma, hay fever, or urticaria. The following adverse reactions have been reported as associated with the use of Ampicillin:

**Gastrointestinal**—Glossitis, stomatitis, black "hairy" tongue, nausea, vomiting, enterocolitis, pseudomembranous colitis and diarrhea. (These reactions are usually associated with oral dosage forms.)

**Hypersensitivity reactions**—An erythematous maculopapular rash has been reported fairly frequently. Urticaria and erythema multiforme have been reported occasionally. A few cases of exfoliative dermatitis have been reported. Anaphylaxis is the most serious reaction experienced and has usually been associated with the parenteral dosage form.

**Note:** Urticaria, other skin rashes, and serum sickness-like reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, Ampicillin should be discontinued unless, in the opinion of the physician, the condition being treated is life-threatening and amenable only to Ampicillin therapy.

**Liver**—A moderate rise in serum glutamic oxaloacetic transaminase (SGOT) has been noted, particularly in infants, but the significance of this finding is unknown.

**Hemic and Lymphatic Systems**—Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia, and agranulocytosis have been reported during therapy with the penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be sensitivity reactions.

#### DOSAGE AND ADMINISTRATION

*Infections of the ear, nose, throat, and lower respiratory tract* due to streptococci, pneumococci, and nonpenicillinase-producing staphylococci, and also those infections of the upper and lower respiratory tract due to *H. influenzae*:

ADULTS: 250 mg every 6 hours.

CHILDREN: 50 mg/kg/day in divided doses every 6 to 8 hours.

*Infections of the genitourinary tract caused by sensitive Gram-negative and Gram-positive bacteria:*

ADULTS: 500 mg every 6 hours. Larger doses may be required for severe infections.

CHILDREN: 100 mg/kg/day in divided doses every 6 hours.

*Uncomplicated urethritis due to N. gonorrhoeae:*

ADULT MALES AND FEMALES: 3.5 grams single oral dose administered simultaneously with 1 gram of probenecid.

*Cases of gonorrhea with a suspected lesion of syphilis should have dark-field examinations before receiving Ampicillin, and monthly serological tests for a minimum of 4 months.*

*Infections of the gastrointestinal tract:*

ADULTS: 500 mg every 6 hours.

CHILDREN: 100 mg/kg/day in divided doses every 6 hours.

Larger doses may be required for stubborn or severe infections. The children's dosage is intended for individuals whose weight will not cause a dosage to be calculated greater than that recommended for adults. Children weighing more than 20 kg should be dosed according to the adult recommendations.

It should be recognized that in the treatment of chronic urinary tract and intestinal infections, frequent bacteriological and clinical appraisals are necessary. Smaller doses than those recommended above should not be used. Even higher doses may be needed at times. In stubborn infections, therapy may be required for several weeks. It may be necessary to continue clinical and/or bacteriological follow-up for several months after cessation of therapy.

Treatment should be continued for a minimum of 48 to 72 hours beyond the time that the patient becomes asymptomatic or evidence of bacterial eradication has been obtained. It is recommended that there be at least 10 days' treatment for any infection caused by hemolytic streptococci, to help prevent the occurrence of acute rheumatic fever or glomerulonephritis.

#### DIRECTIONS FOR MIXING ORAL SUSPENSION

Prepare suspension at time of dispensing as follows: Add the required amount of water (see table below) to the bottle. For ease of preparation, add water in two portions. Shake well after each addition of water. Each teaspoonful (5 ml) will contain 125 mg or 250 mg Ampicillin.

Bottle Size	Amount of Water Required for Reconstitution
80 ml	53 ml
100 ml	66 ml
150 ml	100 ml
200 ml	132 ml

SHAKE WELL BEFORE USING. Keep bottle tightly closed. Any unused portion of the reconstituted suspension must be discarded after 7 days at room temperature or 14 days under refrigeration.

#### HOW SUPPLIED

**TOTACILLIN (Ampicillin) Capsules.** Each capsule contains 250 mg or 500 mg Ampicillin as the trihydrate.

##### 250 mg/Capsule

NDC 0029-6615-25.....bottles of 20  
NDC 0029-6615-28.....bottles of 40  
NDC 0029-6615-30.....bottles of 100  
NDC 0029-6615-32.....bottles of 500  
NDC 0029-6615-31.....unit dose  
cartons of 100

##### 500 mg/Capsule

NDC 0029-6620-25.....bottles of 20  
NDC 0029-6620-28.....bottles of 40  
NDC 0029-6620-29.....bottles of 50  
NDC 0029-6620-32.....bottles of 500  
NDC 0029-6620-31.....unit dose  
cartons of 100

**TOTACILLIN (Ampicillin) for Oral Suspension.** Each 5 ml of reconstituted suspension contains 125 mg or 250 mg Ampicillin as the trihydrate.

##### 125 mg/5 ml

NDC 0029-6625-21..... 80 ml bottle  
NDC 0029-6625-23.....100 ml bottle  
NDC 0029-6625-22.....150 ml bottle  
NDC 0029-6625-24..... 200 ml bottle

##### 250 mg/5 ml

NDC 0029-6630-21..... 80 ml bottle  
NDC 0029-6630-23.....100 ml bottle  
NDC 0029-6630-22.....150 ml bottle  
NDC 0029-6630-24..... 200 ml bottle

**Beecham**  
laboratories

DIV. OF BEECHAM INC. BRISTOL, TENN. 37620

Rev. October 1977

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**Approval Package for:**

**APPLICATION NUMBER:**

**60-666 supplement**

Trade Names: Pen A for Oral Suspension  
125mg/5mL and 250mg/5mL

Generic Name: ampicillin trihydrate

Sponsor: Beecham Laboratories

Approval Date: April 10, 1978

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**CONTENTS**

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**Reviews / Information Included in this ANDA Review.**

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Approval Letter(s)	X
Tentative Approval Letter(s)	
Final Printed Labeling	X
CSO Labeling Review(s)	
Medical Officer Review(s)	
Chemistry Review(s)	
Microbiology Review(s)	
Bioequivalence Review(s)	
Administrative Document(s)	
Correspondence	

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**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**APPROVAL LETTER**

**Beecham**  
laboratories

65 INDUSTRIAL SOUTH, CLIFTON, NEW JERSEY 07012

201-778-9000

REGULATORY DEPARTMENT

CABLE ADDRESS "BEECHPROD"  
TELEX 133471

*OK to sign out  
DJP 4/10/78*

April 5, 1978

Food and Drug Administration  
Certifiable Drug Review Staff (HFD-535)  
Division of Generic Drug Monographs  
Bureau of Drugs  
5600 Fishers Lane  
Rockville, Maryland 20857

*(For use of Food and Drug Administration)*  
*4/10/78*  
*Chas. P. Vadnai*  
For the Commissioner of Food and Drugs  
Food and Drug Administration  
Department of Health, Education, and Welfare

Re: #60-666 (440.107c)

Gentlemen:

Reference is made to Beecham Laboratories' approved Form 6 #60-666 covering Ampicillin for Oral Suspension, distributed by Pfizer Inc. under the trade name Pen A.

We are submitting, in triplicate, a final printed package insert, the "Adverse Reactions" section of which was revised in accordance with Mr. I. David Powers' letter of September 28, 1977 to Beecham Laboratories, and final printed labels which reflect a minor editorial revision.

**RECEIVED**  
**APRIL 10 1978**  
**Food & Drug Admin**  
**Certification Services**

Sincerely,

BEECHAM LABORATORIES

*G. Vadnai / G. Vadnai*

George Vadnai, Ph.D.  
Manager, Governmental Affairs

002376

GSV:dmm  
Enclosures

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**FINAL PRINTED LABELING**



# Pen A<sup>®</sup>



## ampicillin

CAPSULES  
250 mg  
and  
500 mg

for  
ORAL SUSPENSION  
125 mg / 5 ml  
and  
250 mg / 5 ml

### Description

Pen A (ampicillin) is derived from the penicillin nucleus, 6-amino-penicillanic acid (6-APA). Chemically it is D (-)  $\alpha$ -aminobenzyl penicillin trihydrate.

### Actions

#### MICROBIOLOGY:

Pen A (ampicillin) is similar to benzyl penicillin in its bactericidal action against sensitive organisms during the stage of active multiplication. It acts through the inhibition of biosynthesis of cell wall mucopeptide. Pen A (ampicillin) differs in *in vitro* spectrum from benzyl penicillin in the gram-negative spectrum. It exerts high *in vitro* activity against many strains of *Hemophilus influenzae*, *Neisseria gonorrhoeae*, *Neisseria meningitidis* and *Neisseria catarrhalis*, *Escherichia coli*, *Proteus mirabilis*, *Bacteroides funduliformis*, *Salmonellae* and *Shigellae*.

*In vitro* studies have also demonstrated the sensitivity of many strains of the following gram-positive bacteria: alpha- and beta-hemolytic streptococci, *Diplococcus pneumoniae*, nonpenicillinase-producing staphylococci, *Bacillus anthracis*, and most strains of enterococci and clostridia. Ampicillin generally provides less *in vitro* activity than penicillin G against gram-positive bacteria. Because it does not resist destruction by penicillinase, it is not effective against penicillinase-producing bacteria, particularly resistant staphylococci. All strains of *Pseudomonas* and most strains of *Klebsiella* and *Aerobacter* are resistant.

#### PHARMACOLOGY:

Pen A (ampicillin) is acid stable and therefore well absorbed. Food, however, retards absorption. Blood serum levels of approximately 2 mcg/ml are attained within 1-2 hours following a 250 mg oral dose given to fasting adults. Detectable amounts persist for about 6 hours. Pen A (ampicillin) diffuses readily into all body tissues and fluids with the exception of brain and spinal fluid except when meninges are inflamed. Higher serum levels are obtained following I.M. injection. Most of the ampicillin is excreted unchanged in the urine and this excretion can be delayed by concurrent administration of probenecid. The active form appears in the bile in higher concentrations than found in the serum. Pen A (ampicillin) is the least serum bound of all the penicillins, averaging about 20% compared to approximately 60%-90% for other penicillins.

### Indications

Pen A (ampicillin) is indicated in the treatment of infections due to susceptible strains of the following:

*gram-negative organisms*—*Shigellae*, *Salmonellae* (including *S. typhosa*), *H. influenzae*, *E. coli* and *P. mirabilis*, *N. gonorrhoeae*, and *N. meningitidis*;  
*gram-positive organisms*—Streptococci, *D. pneumoniae*, and nonpenicillinase-producing staphylococci.

Because of its wide spectrum and bactericidal action, it may be useful in instituting therapy; however, bacteriological studies to determine the causative organisms and their sensitivity to ampicillin should be performed.

Indicated surgical procedures should be performed.

### Contraindications

A history of allergic reaction to any of the penicillins is a contraindication.

### Warnings

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL THERAPY, IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. THESE REACTIONS ARE MORE APT TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR HYPERSENSITIVITY REACTIONS TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE THERAPY WITH A PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, THE DRUG SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED.

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE, OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

### USAGE IN PREGNANCY:

Safety for use in pregnancy has not been established.

### Precautions

As with any antibiotic preparation, constant observations for signs of overgrowth of nonsusceptible organisms, including fungi, are essential. Should superinfection occur (usually involving *Aerobacter*, *Pseudomonas*, or *Candida*), the drug should be discontinued and/or appropriate therapy instituted. As with any potent agent, it is advisable to check periodically for organ system dysfunc-

*Precautions (continued)*

tion during prolonged therapy; this includes renal, hepatic, and hematopoietic systems. This is particularly important in prematures, neonates and other infants.

**Adverse Reactions**

As with other penicillins, it may be expected that untoward reactions will be essentially limited to sensitivity phenomena. They are more likely to occur in individuals who have previously demonstrated hypersensitivity to penicillins and in those with a history of allergy, asthma, hay fever, or urticaria. The following adverse reactions have been reported as associated with the use of ampicillin:

*Gastrointestinal*—glossitis, stomatitis, black "hairy" tongue, nausea, vomiting, enterocolitis, pseudomembranous colitis, and diarrhea. (These reactions are usually associated with oral dosage forms.)

*Hypersensitivity reactions*—An erythematous maculopapular rash has been reported fairly frequently. Urticaria and erythema multiforme have been reported occasionally. A few cases of exfoliative dermatitis have been reported. Anaphylaxis is the most serious reaction experienced and has usually been associated with the parenteral dosage form.

*Note:* Urticaria, other skin rashes, and serum sickness-like reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, ampicillin should be discontinued, unless, in the opinion of the physician, the condition being treated is life-threatening and amenable only to ampicillin therapy.

*Liver*—A moderate rise in serum glutamic oxaloacetic transaminase (SGOT) has been noted, particularly in infants, but the significance of this finding is unknown.

*Hemic and Lymphatic Systems*—Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia, and agranulocytosis have been reported during therapy with the penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be sensitivity reactions.

**Dosage**

*Infections of the ear, nose, throat, and lower respiratory tract* due to streptococci, pneumococci, and nonpenicillinase-producing staphylococci, and also those infections of the upper and lower respiratory tract due to *H. influenzae*:

Adults— 250 mg every 6 hours.

Children— 50 mg/kg/day in divided doses every 6 or 8 hours.

*Infections of the genitourinary tract caused by sensitive gram-negative and gram-positive bacteria:*

Adults— 500 mg every 6 hours. Larger doses may be required for severe infections.

Children— 100 mg/kg/day in divided doses every 6 hours.

*Uncomplicated urethritis due to N. gonorrhoeae:*

Adult males and females—3.5 grams single oral dose administered simultaneously with 1.0 gram of probenecid.

*Cases of gonorrhea with a suspected lesion of syphilis should have dark field examinations before receiving ampicillin, and monthly serological tests for a minimum of 4 months.*

*Infections of the gastrointestinal tract:*

Adults— 500 mg every 6 hours.

Children— 100 mg/kg/day in divided doses every 6 hours.

Larger doses may be required for stubborn or severe infections. The children's dosage is intended for individuals whose weight will not cause a dosage to be calculated greater than that recommended for adults. Children weighing more than 20 kg should be dosed according to the adult recommendations.

It should be recognized that in the treatment of chronic urinary tract and intestinal infections, frequent bacteriological and clinical appraisals are necessary. Smaller doses than those recommended above should not be used. Even higher doses may be needed at times. In stubborn infections, therapy may be required for several weeks. It may be necessary to continue clinical and/or bacteriological follow-up for several months after cessation of therapy.

Treatment should be continued for a minimum of 48 to 72 hours beyond the time that the patient becomes asymptomatic or evidence of bacterial eradication has been obtained. It is recommended that there be at least 10 days' treatment for any infection caused by hemolytic streptococci, to help prevent the occurrence of acute rheumatic fever or glomerulonephritis.

**Directions for Mixing Oral Suspension**

Prepare suspension at time of dispensing as follows: Add 66 ml of water to the 100 ml package and 132 ml of water to the 200 ml package. Shake vigorously. This will provide 100 and 200 ml of suspension, respectively. Each teaspoonful (5 ml) will contain 125 mg or 250 mg ampicillin. SHAKE WELL BEFORE USING. Keep bottle tightly closed. Any unused portion of the reconstituted suspension must be discarded after 7 days at room temperature or 14 days under refrigeration.

**How Supplied**

Pen A (ampicillin) Capsules: Ampicillin trihydrate equivalent to 250 mg or 500 mg ampicillin per capsule.

250 mg: bottles of 100 and 500.

500 mg: bottles of 100.

Pen A (ampicillin) for Oral Suspension: Each 5 ml of reconstituted suspension contains ampicillin trihydrate equivalent to 125 mg or 250 mg ampicillin.

125 mg/5 ml: bottles of 100 ml and 200 ml.

250 mg/5 ml: bottles of 100 ml and 200 ml.

Manufactured by Beecham Laboratories,  
Div. Beecham Inc., Bristol, TN 37620

Distributed by



PFIZER INC., NEW YORK, N.Y. 10017

60-2373-00-2  
9049/E

Printed in U.S.A.  
Revised Mar. 1978

NDC 0995-0311-44 2394

**Pen A<sup>®</sup>**  
ampicillin  
FOR ORAL  
SUSPENSION

**125 mg / 5 ml<sup>1</sup>**

**100 ml**

equivalent to  
2.5 g ampicillin

CAUTION: Federal law prohibits  
dispensing without prescription.

Distributed by  
 **Pfizer** DIVISION  
PFIZER INC., NEW YORK, N.Y. 10017

**RECOMMENDED STORAGE IN DRY FORM**

**STORE BELOW 86°F. (30°C.)**

<sup>1</sup>When reconstituted as directed each 5 ml (1 teaspoonful)

contains ampicillin trihydrate equivalent to 125 mg ampicillin.

Directions for reconstitution: Add 66 ml of water. For ease

of preparation, tap gently, add water in 2 portions.

Shake well after each addition.

MADE IN U.S.A. 3

EXP.

LOT NO.

**KEEP CONTAINER TIGHTLY CLOSED - SHAKE WELL BEFORE USING**

When suspension is stored at room temperature discard  
unused portion after 7 days; when stored under  
refrigeration discard unused portion after 14 days.

**READ ACCOMPANYING PROFESSIONAL INFORMATION**

**USUAL DOSAGE**-Children: 50 to 100 mg/kg/day in divided  
doses every 6 to 8 hours.

Adults: 250 to 500 mg every 6 hours.

Manufactured by Beecham Laboratories, Div. Beecham Inc., Bristol,  
TN 37620

8022/D

NDC 0995-0311-91 2395

# Pen A<sup>®</sup>

ampicillin  
FOR ORAL  
SUSPENSION  
125 mg/5 ml<sup>†</sup>  
200 ml

equivalent to  
5.0 g ampicillin

CAUTION: Federal law prohibits  
dispensing without prescription.

Distributed by

**Pf** **pharmecs** DIVISION  
PFIZER INC., NEW YORK, N.Y. 10017

**RECOMMENDED STORAGE IN DRY FORM**

STORE BELOW 86° F. (30° C.)

†When reconstituted as directed each 5 ml (1 teaspoonful) contains ampicillin trihydrate, equivalent to 125 mg ampicillin. Directions for reconstitution: Add 132 ml of water. For ease of preparation, tap gently, add water in 2 portions. Shake well after each addition.

MADE IN U.S.A. 3

EXP.

LOT NO.

**KEEP CONTAINER TIGHTLY CLOSED - SHAKE WELL BEFORE USING**

When suspension is stored at room temperature discard unused portion after 7 days; when stored under refrigeration discard unused portion after 14 days.

**READ ACCOMPANYING PROFESSIONAL INFORMATION**

**USUAL DOSAGE**

Children: 50 to 100 mg/kg/day in divided doses every 6 to 8 hours.

Adults: 250 to 500 mg every 6 hours.

Manufactured by Beecham Laboratories, Div. Beecham Inc., Bristol, TN 37620

5016/D

NDC 0995-0312-44 2396

**Pen A<sup>®</sup>**  
ampicillin  
FOR ORAL  
SUSPENSION

**250 mg/5 ml**

**100 ml**

equivalent to  
5.0 g ampicillin

CAUTION: Federal law prohibits  
dispensing without prescription.

Distributed by  
 **Pfizer** DIVISION  
PFIZER INC., NEW YORK, N.Y. 10017

**RECOMMENDED STORAGE IN DRY FORM**

STORE BELOW 86° F. (30° C.)  
When reconstituted as directed each 5 ml (1 teaspoonful)  
contains ampicillin trihydrate equivalent to 250 mg ampicillin.  
Directions for reconstitution: Add 56 ml of water. For ease  
of preparation, tap gently, add water in 2 portions.  
Shake well after each addition. MADE IN U.S.A. 3

EXP.

LOT NO.

**KEEP CONTAINER TIGHTLY CLOSED-SHAKE WELL BEFORE USING**  
When suspension is stored at room temperature discard  
unused portion after 7 days; when stored under  
refrigeration discard unused portion after 14 days.

**READ ACCOMPANYING PROFESSIONAL INFORMATION**  
**USUAL DOSAGE-Children:** 50 to 100 mg/kg/day in divided  
doses every 6 to 8 hours.  
**Adults:** 250 to 500 mg every 6 hours.

Manufactured by Beecham Laboratories, Div. Beecham Inc., Bristol,  
TN 37620

9019/D

NDC 0995-0312-91 2397

# Pen A<sup>®</sup>

ampicillin  
FOR ORAL  
SUSPENSION

**250 mg/5 ml**

**200 ml**  
equivalent to  
10.0 g ampicillin

CAUTION: Federal law prohibits  
dispensing without prescription.

Distributed by  
 **Pfizer** DIVISION  
PFIZER INC., NEW YORK, N.Y. 10017

**RECOMMENDED STORAGE IN DRY FORM**

STORE BELOW 86° F. (30° C.)

When reconstituted as directed each 5 ml (1 teaspoonful) contains ampicillin trihydrate equivalent to 250 mg ampicillin.

Directions for reconstitution: Add 4.32 ml of water. For ease of preparation, tap gently, add water in 2 portions. Shake well after each addition.

MADE IN U.S.A. 3

EXP.

LOT NO.

**KEEP CONTAINER TIGHTLY CLOSED - SHAKE WELL BEFORE USING**  
When suspension is stored at room temperature discard unused portion after 7 days; when stored under refrigeration discard unused portion after 14 days.

READ ACCOMPANYING PROFESSIONAL INFORMATION

**USUAL DOSAGE**

Children: 50 to 100 mg/kg/day in divided doses every 6 to 8 hours.

Adults: 250 to 500 mg every 6 hours.

Manufactured by Beecham Laboratories, Div. Beecham Inc., Bristol, TN 37620

D/10106

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**Approval Package for:**

**APPLICATION NUMBER:**

**60-666 supplement**

Trade Names: Penbritin for Oral Suspension  
125mg/5mL and 250mg/5mL

Generic Name: ampicillin trihydrate

Sponsor: Beecham Laboratories

Approval Date: April 17, 1978

# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:**

**60-666 supplement**

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### Reviews / Information Included in this ANDA Review.

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Approval Letter(s)	X
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Medical Officer Review(s)	
Chemistry Review(s)	
Microbiology Review(s)	
Bioequivalence Review(s)	
Administrative Document(s)	X
Correspondence	X

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**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**APPROVAL LETTER**

**Beecham**  
laboratories

65 INDUSTRIAL SOUTH, CLIFTON, NEW JERSEY 07012

201-778-9000

REGULATORY DEPARTMENT

CABLE ADDRESS "BEECHPROD"  
TELEX 133471

April 11, 1978

*OK to sign out  
JSP 4/17/78*

Food and Drug Administration  
Certifiable Drug Review Staff (HFD-525)  
Division of Generic Drug Monographs  
Bureau of Drugs  
5600 Fishers Lane  
Rockville, Maryland 20857

**For use of Food and Drug Administration**  
*4/17/78*  
*John D. ...*  
**For the Commissioner of Food and Drugs**  
**Food and Drug Administration**  
**Department of Health, Education, and Welfare**

Re: #60-666 (440.107c)

Gentlemen:

Reference is made to Beecham Laboratories' approved Form 6 Antibiotic Application #60-666 covering Ampicillin for Oral Suspension. We hereby wish to supplement our Application to provide for:

1. A revised final printed package insert for the Penbritin brand of Oral Suspension distributed by Ayerst Laboratories. This insert reflects the change in the "Adverse Reactions" section in accordance with Mr. I. David Power's letter of September 28, 1977 to Beecham Laboratories;
2. Notification that \_\_\_\_\_ is \_\_\_\_\_ of the child-resistant safety closure; the specifications are identical to those previously submitted.

This supplement is submitted in triplicate.

Sincerely,

002513

BEECHAM LABORATORIES

*George Vadnai*

George Vadnai, Ph.D.  
Manager, Governmental Affairs

GSV:dmm  
Enclosures

RECEIVED  
APRIL 14 1978  
Food & Drug Administration  
Certification Services

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**FINAL PRINTED LABELING**

**PENBRITIN\***  
(ampicillin)

OS-17

for  
**ORAL SUSPENSION**  
125 mg/5 ml  
and  
250 mg/5 ml

**PEDIATRIC DROPS**  
for  
**ORAL SUSPENSION**  
100 mg/ml

**CAUTION:** Federal law prohibits dispensing without prescription.

**DESCRIPTION**

Chemical name: D(—)-alpha-aminobenzyl penicillin

PENBRITIN is an orally active, semisynthetic broad spectrum penicillin. It is inactivated by penicillinase.

**ACTIONS**

**Microbiologic:**

Ampicillin appears to act primarily by interfering with the synthesis or maintenance of the bacterial cell wall. It strongly inhibits the early lag and logarithmic phases of bacterial multiplication. In *in vitro* studies, ampicillin is bactericidal.

PENBRITIN is effective against the usual penicillin-susceptible gram-positive organisms, and in addition, many gram-negative pathogens. It is active *in vitro* against many strains of the following bacteria:

**GRAM-POSITIVE**—Alpha and beta hemolytic streptococci, nonpenicillinase-producing staphylococci, *Diplococcus pneumoniae*, *Clostridia* species, *Bacillus anthracis*, most strains of enterococci.

**GRAM-NEGATIVE**—*Haemophilus influenzae*, *Neisseria gonorrhoeae* and meningitidis, *Proteus mirabilis*, *Escherichia coli*, *Salmonella* (including *S. typhosa*), *Neisseria catarrhalis*, *Bacteroides funduliformis*, and *Shigella*.

All strains of *Pseudomonas* and most strains of *Klebsiella-Aerobacter* are resistant. Because ampicillin is destroyed by penicillinase, PENBRITIN is not effective against penicillinase-producing bacteria.

**Pharmacologic:**

PENBRITIN is stable in acid and is therefore not destroyed by gastric juice. (Food, however, retards absorption.) PENBRITIN is well absorbed and produces high and persistent blood levels of unbound ampicillin. Ampicillin is the least protein bound of all the penicillins, averaging 20 percent as contrasted with 60 to 90 percent for the others. Blood serum levels of approximately 2 mcg/ml are achieved within one to two hours following a 250 mg oral dose to fasting adults. Detectable amounts persist in the blood for about six hours. There are high concentrations in the bile and urine. Ampicillin diffuses readily into most body tissues and fluids. However, penetration into the cerebral spinal fluid occurs only with meningeal inflammation. Ampicillin is excreted in the urine, largely unchanged, and this excretion can be delayed by concurrent administration of probenecid.

**INDICATIONS**

PENBRITIN is indicated in the treatment of infections due to susceptible strains of the following:

**GRAM-NEGATIVE** organisms: *Shigella*, *Salmonella* (including *S. typhosa*), *H. influenzae*, *E. coli*, *P. mirabilis*, *N. gonorrhoeae*, and *N. meningitidis*.

**GRAM-POSITIVE** organisms: Streptococci, nonpenicillinase-producing staphylococci, and *D. pneumoniae*.

Bacteriologic studies to determine the causative organisms and their sensitivity to ampicillin should be performed. Because PENBRITIN is a broad spectrum antibiotic, therapy may be instituted prior to the results of sensitivity testing.

**CONTRAINDICATIONS**

PENBRITIN is contraindicated in patients with a history of hypersensitivity to any penicillin.

**WARNINGS**

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL THERAPY, IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. THESE REACTIONS ARE MORE APT TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR HYPERSENSITIVITY REACTIONS TO MULTIPLE ALLERGENS.

THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE THERAPY WITH A PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, AND OTHER ALLERGENS.

IF AN ALLERGIC REACTION OCCURS, THE DRUG SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE, OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

USAGE IN PREGNANCY: Safety for use in pregnancy has not been established.

**PRECAUTIONS**

As with any antibiotic preparation, constant observation for signs of overgrowth of nonsusceptible organisms, including fungi, is essential. Should superinfection occur (usually involving *Aerobacter*, *Pseudomonas*, or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.

Periodic assessment of renal, hepatic, and hematopoietic function should be made during prolonged therapy. This is particularly important in prematures, neonates and other infants.

**ADVERSE REACTIONS**

As with other penicillins, it may be expected that untoward reactions will be essentially limited to sensitivity phenomena. These are more likely to occur in individuals with a history of allergy, asthma, hay fever, or urticaria.

The following adverse reactions have been reported as associated with the use of ampicillin:

Gastrointestinal—glossitis, stomatitis, black "hairy" tongue, nausea, vomiting, enterocolitis, pseudomembranous colitis, and diarrhea. (These reactions are usually associated with oral administration.)

# PENBRITIN (ampicillin) for Oral Suspension & Pediatric Drops for Oral Suspension cont'd.

**Hypersensitivity reactions** — erythematous maculopapular rashes have been reported fairly frequently; urticaria, erythema multiforme, and an occasional case of exfoliative dermatitis have been reported. Anaphylaxis is usually associated with parenteral administration.

**Note:** Urticaria, other skin rashes, and serum sickness-like reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, ampicillin should be discontinued unless, in the opinion of the physician, the condition being treated is life-threatening and amenable only to ampicillin therapy.

**Hepatic** — A moderate rise in serum glutamic oxaloacetic transaminase (SGOT) has been noted, particularly in infants. The significance of this finding is unknown.

**Hemic and lymphatic** — anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia, and agranulocytosis have been reported. These are usually reversible on discontinuation of the drug, and are believed to be hypersensitivity phenomena.

## DOSAGE AND ADMINISTRATION

Infection	Usual Dosage* Adults	Usual Dosage* Children†
Respiratory tract	250 mg q 6 hours	50 mg/kg/day in equal doses q 6-8 hours
Gastrointestinal tract Genitourinary tract	500 mg q 6 hours	100 mg/kg/day in equal doses q 6-8 hours
Urethritis in Males or Females due to <i>N. gonorrhoeae</i>	3.5 g single oral dose administered simultaneously with 1.0 g of probenecid	

In the treatment of complications of gonorrheal urethritis, such as prostatitis and epididymitis, prolonged and intensive therapy is recommended.

Cases of gonorrhea with a suspected primary lesion of syphilis should have dark-field examinations before receiving treatment. In all other cases where concomitant syphilis is suspected, monthly serologic tests should be made for a minimum of four months.

\*Larger than usual dosages may be required for stubborn or severe infections. Smaller doses than those recommended above should not be used.

†The children's dosage is intended for individuals whose weight will not cause a dosage to be calculated greater than that recommended for adults. Children weighing more than 20 kg (44 lb) should be given the adult recommended dosage.

## PEDIATRIC DROPS:

A suggested dosage regimen is:  
 Under 12 lb — 0.6 ml q 6 hours  
 12-25 lb — 1.0 ml q 6 hours  
 25-44 lb — 2.0 ml q 6 hours

**DURATION OF TREATMENT:** Medications should be continued for at least 48 to 72 hours after all symptoms have subsided or cultures have become negative. For any infection caused by hemolytic streptococci, at least 10 days of treatment is recommended to help prevent the occurrence of acute rheumatic fever or glomerulonephritis.

## DIRECTIONS FOR MIXING ORAL SUSPENSIONS

Prepare suspensions at time of dispensing as follows: Add the required amount of water (see table below) to the bottle and shake vigorously. Each teaspoonful (5 ml) of reconstituted Oral Suspension will contain 125 mg or 250 mg ampicillin, depending upon the initial concentration. Each ml of reconstituted Pediatric Drops will contain 100 mg ampicillin.

Bottle Size	Amount of Water Required for Reconstitution
100 ml Oral Suspension	66 ml
200 ml Oral Suspension	132 ml
20 ml Pediatric Drops	11.5 ml

SHAKE WELL BEFORE USING.

## STABILITY

**ORAL SUSPENSION:** No refrigeration required before mixing. After mixing, suspension may be kept at room temperature [21.1° C (70° F)] for 7 days or in a refrigerator [4.4° C (40° F)] for 14 days without significant loss of potency. KEEP TIGHTLY CLOSED.

**PEDIATRIC DROPS:** No refrigeration required before mixing. After mixing, suspension may be kept in a refrigerator for 14 days without significant loss of potency. KEEP TIGHTLY CLOSED.

## HOW SUPPLIED

**PENBRITIN (ampicillin) for Oral Suspension** — when reconstituted:

Each 5 ml (one teaspoonful) contains 125 mg ampicillin as the trihydrate. Bottles for 100 ml (NDC 0046-0607-86) and 200 ml (NDC 0046-0607-82).

Each 5 ml (one teaspoonful) contains 250 mg ampicillin as the trihydrate. Bottles for 100 ml (NDC 0046-0611-86) and 200 ml (NDC 0046-0611-82).

**PENBRITIN (ampicillin) PEDIATRIC DROPS for Oral Suspension** — when reconstituted:

Each ml contains 100 mg ampicillin as the trihydrate. Bottles for 20 ml (NDC 0046-0625-20).

Distributed by  
**AYERST LABORATORIES INCORPORATED**  
 New York, N.Y. 10017

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**ADMINISTRATIVE  
DOCUMENT(S)**

<b>NOTICE OF APPROVAL NEW DRUG APPLICATION OR SUPPLEMENT</b>		NDA NUMBER <i>60-666</i>
		DATE APPROVAL LETTER ISSUED <i>4/17/78</i>
TO: Press Relations Staff (HFI-40)	FROM:	<input checked="" type="checkbox"/> Bureau of Drugs <input type="checkbox"/> Bureau of Veterinary Medicine
ATTENTION Forward original of this form for publication only after approval letter has been issued and the date of approval has been entered above.		
TYPE OF APPLICATION <input type="checkbox"/> ORIGINAL NDA <input checked="" type="checkbox"/> SUPPLEMENT TO <del>NDA</del> <i>FORM 6</i> <input type="checkbox"/> ABBREVIATED ORIGINAL NDA <input type="checkbox"/> SUPPLEMENT TO ANDA		CATEGORY <input checked="" type="checkbox"/> HUMAN <input type="checkbox"/> VETERINARY
TRADE NAME (or other designated name) AND ESTABLISHED OR NONPROPRIETARY NAME (if any) OF DRUG <i>AMPICILLIN</i>		
DOSAGE FORM <i>for ORAL SUSPENSION</i>		HOW DISPENSED <input checked="" type="checkbox"/> RX <input type="checkbox"/> OTC
ACTIVE INGREDIENT(S) (as declared on label. List by established or nonproprietary name(s) and include amount(s), if amount is declared on label.) <i>AMPICILLIN (as the trihydrate) - 125 mg / 5 ml 250 mg / 5 ml 100 mg / ml</i>		
NAME OF APPLICANT (Include City and State) <i>BEECHAM LABORATORIES CLIFTON, N. J.</i>		
PRINCIPAL INDICATION OR PHARMACOLOGICAL CATEGORY <i>ANTIBACTERIAL</i>		
COMPLETE FOR VETERINARY ONLY		
ANIMAL SPECIES FOR WHICH APPROVED		
COMPLETE FOR SUPPLEMENT ONLY		
CHANGE APPROVED TO PROVIDE FOR <i>DISTRIBUTOR REVISED PACKAGE INSERT ALTERNATE SUPPLIER</i>		
FORM PREPARED BY NAME <i>J. David Powers</i>		DATE <i>4/17/78</i>
FORM APPROVED BY NAME <i>John E. Barum</i>		DATE <i>4/17/78</i>

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**CORRESPONDENCE**



DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE  
 PUBLIC HEALTH SERVICE  
 FOOD AND DRUG ADMINISTRATION  
 ROCKVILLE, MARYLAND 20857

April 7, 1978

*7-6 jacket*

Our Reference:

60-675

Sheila A. Scolnick  
 Quality Control Supervisor  
 BEECHAM LABORATORIES  
 101 Possumtown Road  
 Piscataway, New Jersey 08854

Dear Ms. Scolnick:

This is in reference to your Form 7 submission of Ampicillin Trihydrate (bulk), batch mark number 710349R, submitted to us on January 23, 1978 for certification.

Our laboratory report for potency and \_\_\_\_\_ titrations are listed below:

Original Sample

<u>Potency - mcg/mg</u>		<u>%</u>	<u>%</u>
Weight 1 - _____	Weight 4 - _____	_____	_____
Weight 2 - _____	Weight 5 - _____	_____	_____
Weight 3 - _____	Weight 6 - _____	_____	_____
Average - _____			
Corrected - _____			
Concordance - Potency vs. _____			

Additional Sample

<u>Potency - mcg/mg</u>	<u>%</u>	<u>%</u>
Weight 1 - _____	_____	_____
Weight 2 - _____	_____	_____
Weight 3 - _____	_____	_____
Average - _____	Average - _____	Average - _____
Corrected - _____		
Concordance - Potency vs. _____		



**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**Approval Package for:**

**APPLICATION NUMBER:**

**60-666 supplement**

Trade Names: Alpen for Oral Suspension  
125mg/5mL and 250mg/5mL

Generic Name: ampicillin trihydrate

Sponsor: Beecham Laboratories

Approval Date: June 7, 1978

# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:**

**60-666 supplement**

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CSO Labeling Review(s)	
Medical Officer Review(s)	
Chemistry Review(s)	
Microbiology Review(s)	
Bioequivalence Review(s)	
Administrative Document(s)	
Correspondence	

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**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**APPROVAL LETTER**

**Beecham**  
laboratories

65 INDUSTRIAL SOUTH, CLIFTON, NEW JERSEY 07012

201-778-9000

REGULATORY DEPARTMENT

CABLE ADDRESS "BEECHPROD"  
TELEX 133471

June 1, 1978

Date *Notes 6/1/78*

Account No.

*John D. Harrison*  
Department of Health and Human Services  
Food and Drug Administration

Food and Drug Administration  
Certifiable Drug Review Staff (HFD-535)  
Division of Generic Drug Monographs  
Bureau of Drugs  
5600 Fishers Lane  
Rockville, Maryland 20857

Re: #60-666 (440.107c)

Gentlemen:

Reference is made to Beecham Laboratories' approved Form 6 #60-666, covering Ampicillin for Oral Suspension, distributed by Lederle Laboratories under the trade name Alpen.

Please note that Beecham is no longer manufacturing Ampicillin for Lederle Laboratories; however, the Alpen for Oral Suspension supplies remaining on the market will continue to be distributed.

This supplement is submitted in triplicate.

Sincerely,

BEECHAM LABORATORIES

*George Vadnai*

George Vadnai, Ph.D.  
Manager, Governmental Affairs

GSV:dmm

RECEIVED  
JUN 5 1 57 PM '78  
FDA/BD/HFD-535

003250

*Ab Harrison*

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**Approval Package for:**

**APPLICATION NUMBER:**

**60-666 supplement**

Trade Names: Totacillin for Oral Suspension  
125mg/5mL and 250mg/5mL

Generic Name: ampicillin trihydrate

Sponsor: Beecham Laboratories

Approval Date: October 20, 1978

# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:**

**60-666 supplement**

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### Reviews / Information Included in this ANDA Review.

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Approval Letter(s)	X
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Medical Officer Review(s)	
Chemistry Review(s)	
Microbiology Review(s)	
Bioequivalence Review(s)	X
Administrative Document(s)	X
Correspondence	X

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**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**APPROVAL LETTER**

Harrison

# Beecham laboratories

65 INDUSTRIAL SOUTH, CLIFTON, NEW JERSEY 07012

201-778-9000

REGULATORY DEPARTMENT

CABLE ADDRESS "BEECHPROD"  
TELEX 133471

June 20, 1978

Date Approved 10/20/78

Account No. \_\_\_\_\_

Food and Drug Administration  
Certifiable Drug Review Staff (HFD-535)  
Division of Generic Drug Monographs  
Bureau of Drugs  
5600 Fishers Lane  
Rockville, Maryland 20857

Signed [Signature]  
For the ~~Commissioner~~ Department of Health, Education and Welfare  
Department of Health, Education and Welfare

Re: #60-666 (440.107c)

Gentlemen:

Reference is made to Beecham Laboratories' Form 6 Antibiotic Application for Totacillin (ampicillin) for Oral Suspension.

We hereby supplement the above Application to provide for the results and raw data of the bioequivalency study for which the protocols were filed on April 10, 1978.

This supplement is submitted in triplicate.

Sincerely,

BEECHAM LABORATORIES

[Signature]  
George Vadnai, Ph. D.  
Manager, Governmental Affairs

003527

RECEIVED  
JUN 23 1 28 PM '78  
FDA/BD  
HFD-535

GSV:dmm  
Enclosures

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**BIOEQUIVALENCE  
REVIEW(S)**

Totacillin (ampicillin) Oral Suspension  
125 mg/5 ml and 250 mg/5 ml  
Form 6 #60-666

Beecham Laboratories  
Clifton, New Jersey  
Submission Dated:  
April 10, 1978

### REVIEW OF TWO BIOAVAILABILITY PROTOCOLS

Ampicillin is a semi-synthetic penicillin with broad spectrum activity. It is stable in acid and well absorbed in the gastrointestinal tract.

#### OBJECTIVES:

To compare the serum levels of Ampicillin, Beecham, 125 mg/5 ml to Ampicillin, Bristol, 125 mg/5 ml.

#### PROTOCOL I:

This is a two-way crossover design study, using 12 male subjects between 18-55 years of age, within  $\pm 10\%$  of the normal weight-height table, free from other medication for one week and during the study. Subjects will be screened for any history of serious disease and sensitivity to penicillin. They will be tested clinically using CBC, SMA-12, and urinalysis tests. Subjects will fast for eight hours before and 2 hours after dosing. A single dose of 250 mg/10 ml of Ampicillin, Beecham, 125 mg/5 ml or Ampicillin, Bristol, 125 mg/5 ml will be administered with 4 oz of water. 240 ml of water will be given 1-2 hours before dosing and 120 ml of liquid every hour during the study. Blood samples (15 ml) will be collected at 0, 0.33, 0.66, 1, 1.5, 2, 4, and 6 hours, refrigerated at 5°C for 1/2 hour, centrifuged, and the serum separated into 2 three ml portions and frozen and shipped in dry ice to Beecham Laboratories, Bristol, TN. Urine will be collected before dosing and then from 0-6 hours, 5 ml from each collection will be put in sterile tubes for assay. Raw data will be analyzed by an appropriate statistical method. Informed consent forms will be signed by all subjects. The study will be done under the direction of \_\_\_\_\_ and samples assayed at \_\_\_\_\_

#### PROTOCOL II:

This protocol is the same as Protocol I with the exception that the drugs tested will be Ampicillin, Beecham, 250 mg/5 ml and Ampicillin, Bristol, 250 mg/5 ml.

#### COMMENTS: (Protocols I and II)

The drugs should be tested for potency and the lot numbers recorded. The test drugs, Beecham, 125 mg/5 ml and 250 mg/5 ml should be from a production batch. The blood chemistry of subjects should include a hemoglobin and hematocrit and the urinalysis of a microscopic examination. A full description of the analytical microbiological method should be submitted with validation data to assure that the method can measure the drug and/or metabolites expected in the clinical specimens with the required sensitivity, linearity and specificity. This should include

zone sizes, standard curves, etc. The firm should be told that a three-way crossover design study would be adequate. Beecham's, Ampicillin, 125 mg/5 ml x 2 and 250 mg/5 ml compared to Bristols', Ampicillin, 250 mg/5 ml would be sufficient.

RECOMMENDATION:

The firm should be notified of our comments.

*Joseph J. McGuire*  
Joseph J. McGuire  
Biopharmaceutics Review Branch

cc: Form 6 orig., hfd-530, hfd-522, hfd-525, chronological file

JJMCUIRE/lj 7/5/78

RD INITIALED BY HRMURDOCK

FINAL TYPE INITIALED BY *HRM*

APPEARS THIS WAY  
ON ORIGINAL

Totacillin (ampicillin)  
Oral Suspension  
125 mg/5 ml  
FORM 6 60-666

Beecham Laboratories  
Clifton, New Jersey  
Submission Dated:  
June 20, 1978

REVIEW OF A BIOAVAILABILITY STUDY (2)

Ampicillin is a synthetic penicillin with broad spectrum activity, and is effective against penicillin susceptible gram-negative and gram positive organisms.

OBJECTIVES:

To compare Totacillin, 125 mg/5 ml oral suspension (A) to Polycillin 125 mg/5 ml Bristol (B) and Totacillin 250 mg/5 ml (C) to Polycillin 250 mg/5 ml (D) Bristol.

PROTOCOL:

These were two two-way crossover design studies, using 12 male volunteers in each study, weighing between 129-200 pounds, 18 to 39 years of age, screened for any history of serious diseases or sensitivity to penicillin and adequately tested clinically. A single dose of 250 mg was administered to subjects in both studies. Subjects fasted before the initial dose and 2 hours after drug administration. They drank 120 ml of water per hour during the test period. Blood samples (15 ml) were drawn at 0, 0.33, 0.66, 1.0, 1.5, 2, 4 and 6 hours. Urine was collected prior to drug administration, and the 0-6 hours. Two 5 ml aliquots were retained for assay. Clinical specimens were assayed by the \_\_\_\_\_ method using \_\_\_\_\_ The study was conducted at \_\_\_\_\_ under the direction of \_\_\_\_\_

**APPEARS THIS WAY  
ON ORIGINAL**

TEST DRUGS

A	Totacillin	125 mg/5 ml	Lot #HM-2973
B	Polycillin	125 mg/5 ml	Lot #E-5-V-09
C	Totacillin	250 mg/5 ml	Lot #HW-1257
D	Polycillin	250 mg/5 ml	Lot #E-5-V-10

	<u>A</u>	<u>B</u>	<u>C</u>	<u>D</u>
Cmax (mcg/ml)	2.32	2.7	3.2	2.65
Tmax (hour)	1.0	1.0	1.0	1.5
AUC 0-6 mcg-hr/ml	6.29	7.27	7.29	8.22
Urinary Excretion (mg)	177.3	109.8	134.6	109.6

BLOOD LEVEL DATA MCG/ML (MEAN)

<u>TIME (hour)</u>	<u>A</u>	<u>B</u>	<u>C</u>	<u>D</u>
0	0	0	0	0
0.33	0.62 (73%)*	0.96 (86%)*	0.80 (35%)*	0.79 (49%)*
0.66	1.76 (41%)	2.23 (46%)	2.34 (11%)	2.19 (45%)
1.0	2.32 (20%)	2.72 (36%)	3.20 (17%)	2.60 (39%)
1.5	2.44 (30%)	2.52 (27%)	2.05 (24%)	2.65 (29%)
2.0	1.96 (32%)	1.98 (30%)	2.01 (34%)	2.61 (23%)
4.0	0.45 (53%)	0.54 (61%)	0.58 (58%)	0.67 (40%)
6.0	0.14 (46%)	0.25 (28%)	0.20 (43%)	0.29 (69%)

\* Coefficient of variation.

COMMENTS:

These data are in agreement with previously submitted studies.

RECOMMENDATIONS:

The firm should be notified that the study is acceptable and bioequivalency has been established for Beecham's Laboratories', 125 mg/5 ml and 250 mg/5 ml oral suspension.

*Joseph J. McGuire*  
 Joseph J. McGuire  
 Biopharmaceutics Review Branch

cc: Form 6 Orig., HFD-530, HFD-522, HFD-525, Chron File

JJMCGUIRE/mr/9/28/78

RD INITIALED BY SVDIGHE

FINAL TYPE INITIALED BY SVD

10/11/78

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**ADMINISTRATIVE  
DOCUMENT(S)**

MEMO RECORD	AVOID ERRORS PUT IT IN WRITING	DATE 7-20-78
FROM: HFD-531	OFFICE	
TO: File # 60-666	DIVISION	
SUBJECT: Review of Bioavailability Protocol		
<p>SUMMARY</p> <p>Ampicillin trihydrate for Oral Suspension</p> <p style="text-align: right;">sponsor: Beecham Labs Witter, N.J.</p> <p>The subject protocol was received April 12, 1978, we received the review on July 18<sup>th</sup>, 1978, the review is now considered to be "after the fact" since the firm submitted the study on June 27, 1978. The study is currently under review by the Biopharmaceutical Review Branch.</p> <p style="text-align: right;">File WEM</p>		
SIGNATURE WEM	DOCUMENT NUMBER	

# MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION

TO : Jerome P. Skelly, Ph.D.  
Biopharmaceuticals Review Branch (HFD-522)

DATE: June 27, 1978

FROM : Director  
Division of Generic Drug Monographs (HFD-530)

SUBJECT: Bioavailability Study Form 6 #60-666 Ampicillin Trihydrate for Oral Suspension

Sponsor: Beecham Laboratories  
Clifton, New Jersey

On April 14, 1978, we forwarded to your attention Beecham's proposed protocol for a study to be done on their ampicillin for oral suspension. As of this date we have not received your comments on this submission.

Since Beecham holds an approved Form 6 for this product and the test drugs are from certified batches, we are not sure why the study was submitted. Please review and comment.

  
Marvin Seife, M.D.

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**CORRESPONDENCE**



DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
ROCKVILLE, MARYLAND 20857  
October 20, 1978

Our reference:  
60-666 (440.107c)

Beecham Laboratories  
Attention: George Vadnai, Ph.D.  
65 Industrial South  
Clifton, New Jersey 07012

Gentlemen:

This is in reference to your submission of June 20, 1978, consisting of a bioequivalence study conducted on your ampicillin for oral suspension. The study has been reviewed by our Biopharmaceutics Review Branch and found to be satisfactory. An approved copy is enclosed for your files.

Sincerely yours,

*Marvin Seife* 10/20/78

Marvin Seife, M.D.  
Director  
Division of Generic Drug Monographs  
Bureau of Drugs

Enclosure

cc: NWK-DO  
HFD-535 ✓  
HFD-535/OD  
HFD-430/lab.  
HFD-530/Dr. Seife  
WEMagner:hb

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**Approval Package for:**

**APPLICATION NUMBER:**

**60-666 supplement**

Trade Name: Totacillin for Oral Suspension  
125mg/5mL and 150mg/5mL

Generic Name: ampicillin trihydrate

Sponsor: Beecham Laboratories

Approval Date: February 14, 1979

# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:**

**60-666 supplement**

## CONTENTS

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### Reviews / Information Included in this ANDA Review.

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Approval Letter(s)	X
Tentative Approval Letter(s)	
Final Printed Labeling	X
CSO Labeling Review(s)	
Medical Officer Review(s)	
Chemistry Review(s)	
Microbiology Review(s)	
Bioequivalence Review(s)	
Administrative Document(s)	
Correspondence	

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**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**APPROVAL LETTER**

**Beecham**  
laboratories

65 INDUSTRIAL SOUTH, CLIFTON, NEW JERSEY 07012

20T-778-9000

REGULATORY DEPARTMENT

CABLE ADDRESS "BEECHPROD"  
TELEX 133471

2/14/79

*John D. Cassano*

February 8, 1979

*OK to sign out  
JDP 2/13/79*

Food and Drug Administration  
Certifiable Drug Review Staff (HFD-535)  
Division of Generic Drug Monographs  
Bureau of Drugs  
5600 Fishers Lane  
Rockville, Maryland 20857

Re: #60-666 (440.107c)

Gentlemen:

Reference is made to Beecham Laboratories' approved Form 6 Antibiotic Application for Totacillin (ampicillin) for Oral Suspension. We hereby wish to supplement our Application to provide for final printed labeling reflecting a slight revision in the "Directions for Mixing" section.

This supplement is submitted in triplicate.

Sincerely,

BEECHAM LABORATORIES

006350

*Geri Besta*

Geri Besta  
Regulatory Affairs Coordinator

RECEIVED  
FEB 13 8 19 AM '79  
FDA/BDR/HFD-535

Enclosures

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**FINAL PRINTED LABELING**

**Beecham**  
laboratories

**TOTACILLIN<sup>®</sup>**  
ampicillin

CAPSULES  
250 mg  
and  
500 mg

for  
ORAL SUSPENSION  
125 mg/5 ml  
and  
250 mg/5 ml

**DESCRIPTION**

TOTACILLIN (Ampicillin) is derived from the penicillin nucleus, 6-aminopenicillanic acid (6-APA), isolated by Beecham. Chemically it is D (-)  $\alpha$ -aminobenzyl penicillin trihydrate.

**ACTIONS**

**MICROBIOLOGY:**

TOTACILLIN (Ampicillin) is similar to benzyl penicillin in its bactericidal action against sensitive organisms during the stage of active multiplication. It acts through the inhibition of biosynthesis of cell wall mucopeptide. TOTACILLIN (Ampicillin) differs in *in vitro* spectrum from benzyl penicillin in the Gram-negative spectrum. It exerts high *in vitro* activity against many strains of *Haemophilus influenzae*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Neisseria catarrhalis*, *Escherichia coli*, *Proteus mirabilis*, *Bacteroides funduliformis*, *Salmonellae* and *Shigellae*.

*In vitro* studies have also demonstrated the sensitivity of many strains of the following Gram-positive bacteria: alpha- and beta-hemolytic streptococci, *Diplococcus pneumoniae*, nonpenicillinase-producing staphylococci, *Bacillus anthracis*, and most strains of enterococci and clostridia. Ampicillin generally provides less *in vitro* activity than penicillin G against Gram-positive bacteria. Because it does not resist destruction by penicillinase, it is not effective against penicillinase-producing bacteria, particularly resistant staphylococci. All strains of *Pseudomonas* and most strains of *Klebsiella* and *Aerobacter* are resistant.

**PHARMACOLOGY:**

TOTACILLIN (Ampicillin) is acid stable and, therefore, well absorbed. Food, however, retards absorption. Blood serum levels of approximately 2 mcg/ml are attained within 1-2 hours following a 250 mg oral dose given to fasting adults. Detectable amounts persist for about 6 hours.

TOTACILLIN (Ampicillin) diffuses readily into all body tissues and fluids with the exception of brain and spinal fluid except when meninges are inflamed. Higher serum levels are obtained following I.M. injection. Most of the Ampicillin is excreted unchanged in the urine and this excretion can be delayed by concurrent administration of probenecid. The active form appears in the bile in higher concentrations than found in the serum. TOTACILLIN (Ampicillin) is one of the least serum bound of all the penicillins averaging about 20% compared to approximately 60%-90% for other penicillins.

**INDICATIONS**

TOTACILLIN (Ampicillin) is indicated in the treatment of infections due to susceptible strains of the following:

Gram-negative Organisms: *Shigellae*, *Salmonellae* (including *S. typhosa*), *H. influenzae*, *E. coli*, *P. mirabilis*, *N. gonorrhoeae*, and *N. meningitidis*.

Gram-positive Organisms: Streptococci, *D. pneumoniae*, and nonpenicillinase-producing staphylococci.

Because of its wide spectrum and bactericidal action, it may be useful in instituting therapy; however, bacteriological studies to determine the causative organisms and their sensitivity to Ampicillin should be performed. Indicated surgical procedures should be performed.

**CONTRAINDICATIONS**

A history of allergic reaction to any of the penicillins is a contraindication.

**WARNINGS**

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL THERAPY, IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. THESE REACTIONS ARE MORE APT TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR HYPERSENSITIVITY REACTIONS TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE THERAPY WITH A PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, THE DRUG SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE, OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

**USAGE IN PREGNANCY:**

Safety for use in pregnancy has not been established.

(continued from other side)

### ADVERSE REACTIONS

As with other penicillins, it may be expected that untoward reactions will be essentially limited to sensitivity phenomena. They are more likely to occur in individuals who have previously demonstrated hypersensitivity to penicillins and in those with a history of allergy, asthma, hay fever, or urticaria. The following adverse reactions have been reported as associated with the use of Ampicillin:

**Gastrointestinal**—Glossitis, stomatitis, black "hairy" tongue, nausea, vomiting, enterocolitis, pseudomembranous colitis and diarrhea. (These reactions are usually associated with oral dosage forms.)

**Hypersensitivity reactions**—An erythematous maculopapular rash has been reported fairly frequently. Urticaria and erythema multiforme have been reported occasionally. A few cases of exfoliative dermatitis have been reported. Anaphylaxis is the most serious reaction experienced and has usually been associated with the parenteral dosage form.

**Note:** Urticaria, other skin rashes, and serum sickness-like reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, Ampicillin should be discontinued unless, in the opinion of the physician, the condition being treated is life-threatening and amenable only to Ampicillin therapy.

**Liver**—A moderate rise in serum glutamic oxaloacetic transaminase (SGOT) has been noted, particularly in infants, but the significance of this finding is unknown.

**Hemic and Lymphatic Systems**—Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia, and agranulocytosis have been reported during therapy with the penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be sensitivity reactions.

### DOSAGE AND ADMINISTRATION

**Infections of the ear, nose, throat, and lower respiratory tract** due to streptococci, pneumococci, and nonpenicillinase-producing staphylococci, and also those infections of the upper and lower respiratory tract due to *H. influenzae*:

ADULTS: 250 mg every 6 hours.  
CHILDREN: 50 mg/kg/day in divided doses every 6 to 8 hours.

**Infections of the genitourinary tract caused by sensitive Gram-negative and Gram-positive bacteria:**

ADULTS: 500 mg every 6 hours. Larger doses may be required for severe infections.  
CHILDREN: 100 mg/kg/day in divided doses every 6 hours.

**Uncomplicated urethritis due to *N. gonorrhoeae*:**

ADULT MALES AND FEMALES: 3.5 grams single oral dose administered simultaneously with 1 gram of probenecid.

**Cases of gonorrhea with a suspected lesion of syphilis should have dark-field examinations before receiving Ampicillin, and monthly serological tests for a minimum of 4 months.**

**Infections of the gastrointestinal tract:**

ADULTS: 500 mg every 6 hours.  
CHILDREN: 100 mg/kg/day in divided doses every 6 hours.

Larger doses may be required for stubborn or severe infections. The children's dosage is intended for individuals whose weight will not cause a dosage to be calculated greater than that recommended for adults. Children weighing more than 20 kg should be dosed according to the adult recommendations.

It should be recognized that in the treatment of chronic urinary tract and intestinal infections, frequent bacteriological and clinical appraisals are necessary. Smaller doses than those recommended above should not be used. Even higher doses may be needed at times. In stubborn infections, therapy may be required for several weeks. It may be necessary to continue clinical and/or bacteriological follow-up for several months after cessation of therapy.

Treatment should be continued for a minimum of 48 to 72 hours beyond the time that the patient becomes asymptomatic or evidence of bacterial eradication has been obtained. It is recommended that there be at least 10 days' treatment for any infection caused by hemolytic streptococci, to help prevent the occurrence of acute rheumatic fever or glomerulonephritis.

### DIRECTIONS FOR MIXING ORAL SUSPENSION

Prepare suspension at time of dispensing as follows: Tap bottle until all powder flows freely. Add approximately 1/3 of the total amount of water for reconstitution (see table below) and shake vigorously to wet powder. Add the remainder of the water and again shake vigorously. Each teaspoonful (5 ml) will contain 125 mg or 250 mg Ampicillin.

<u>Bottle Size</u>	<u>Amount of Water Required for Reconstitution</u>
80 ml	53 ml
100 ml	66 ml
150 ml	100 ml
200 ml	132 ml

SHAKE WELL BEFORE USING. Keep bottle tightly closed. Any unused portion of the reconstituted suspension must be discarded after 7 days at room temperature or 14 days under refrigeration.

### HOW SUPPLIED

**TOTACILLIN (Ampicillin) Capsules.** Each capsule contains 250 mg or 500 mg Ampicillin as the trihydrate.

#### 250 mg/Capsule

NDC 0029-6615-25.....bottles of 20  
NDC 0029-6615-28.....bottles of 40  
NDC 0029-6615-30.....bottles of 100  
NDC 0029-6615-32.....bottles of 500  
NDC 0029-6615-31.....unit dose  
cartons of 100

#### 500 mg/Capsule

NDC 0029-6620-25.....bottles of 20  
NDC 0029-6620-28.....bottles of 40  
NDC 0029-6620-29.....bottles of 50  
NDC 0029-6620-32.....bottles of 500  
NDC 0029-6620-31.....unit dose  
cartons of 100

**TOTACILLIN (Ampicillin) for Oral Suspension.** Each 5 ml of reconstituted suspension contains 125 mg or 250 mg Ampicillin as the trihydrate.

#### 125 mg/5 ml

NDC 0029-6625-21.....80 ml bottle  
NDC 0029-6625-23.....100 ml bottle  
NDC 0029-6625-22.....150 ml bottle  
NDC 0029-6625-24.....200 ml bottle

#### 250 mg/5 ml

NDC 0029-6630-21.....80 ml bottle  
NDC 0029-6630-23.....100 ml bottle  
NDC 0029-6630-22.....150 ml bottle  
NDC 0029-6630-24.....200 ml bottle

**Beecham**  
laboratories

**KEEP TIGHTLY CLOSED • SHAKE WELL BEFORE USING**  
Any unused portion of the reconstituted suspension must be discarded after 7 days at room temperature or 14 days under refrigeration.

Control No.

Exp. Date

See along perforation

**BEECHAM LABORATORIES**  
DIV. OF BECHTEL INC. BRISTOL, N.Y. 11560

**STORE DRY POWDER AT ROOM TEMPERATURE**

**CAUTION:** Federal law prohibits dispensing without prescription.

NDC 0029-6625-21

**TOTACILLIN®**  
ampicillin

for oral suspension

Equivalent to  
2.0 Gm Ampicillin  
When reconstituted  
each 5 ml will contain

**125 mg**

Ampicillin as the trihydrate

80 ml

**Beecham**  
laboratories

**DIRECTIONS FOR MIXING:**  
Sip bottle until all powder flows freely. Add approximately 1/3 of the total amount of water for reconstitution (total = 53 ml) and shake vigorously to wet powder. Add the remainder of the water and again shake vigorously. Each 5 ml (1 teaspoonful) will then contain Ampicillin trihydrate equivalent to 125 mg Ampicillin.

**USUAL DOSAGE:**

Children: 50-100 mg/kg/day in divided doses every 6-8 hours.  
Adults: 250-500 mg every 6 hours.

**READ ACCOMPANYING INSERT BEFORE USE**

630670

KEEP TIGHTLY CLOSED. • SHAKE WELL BEFORE USING  
Any unused portion of the reconstituted suspension must be  
discarded after 7 days at room temperature or 14 days under  
refrigeration.

Control No.  
Exp. Date

See along perforation

BEECHAM LABORATORIES  
DIV. OF BEECHAM INC. BRISTOL, TENN. 37620

STORE DRY. POWDER AT ROOM TEMPERATURE

CAUTION: Federal law prohibits dispensing without prescrip-  
tion.

NDC 0029-6625-23

**TOTACILLIN®**  
ampicillin  
for oral suspension

Equivalent to  
2.5 Gm Ampicillin

When reconstituted  
each 5 ml will contain

**125 mg**

Ampicillin as the trihydrate

100 ml

**Beecham**  
laboratories

**DIRECTIONS FOR MIXING:**  
Tap bottle until all powder flows freely. Add approximately 1/3  
of the total amount of water for reconstitution (total = 66 ml)  
and shake vigorously to wet powder. Add the remainder of the  
water and again shake vigorously. Each 5 ml (1 teaspoonful)  
will contain Ampicillin Trihydrate equivalent to 125 mg  
Ampicillin.

**USUAL DOSAGE:**  
Children: 50-100 mg/kg/day in divided doses every 6-8 hours.  
Adults: 250-500 mg every 6 hours.

**READ ACCOMPANYING INSERT BEFORE USE**  
6446/D

**KEEP TIGHTLY CLOSED • SHAKE WELL BEFORE USING**  
Any unused portion of the reconstituted suspension must be discarded after 7 days at room temperature or 4 days under refrigeration.

Control No.

Exp. Date

Tear along perforation

**BEECHAM LABORATORIES**

DIV. OF BEECHAM INC., BRISTOL, TENN. 37620

**STORE DRY, POWDER AT ROOM TEMPERATURE**

**CAUTION:** Federal law prohibits dispensing without prescription.

NDC 0029-6625-22

**TOTACILLIN®**  
ampicillin

for oral suspension

Equivalent to  
3.75 Gm. Ampicillin  
When reconstituted  
each 5 ml. will contain

**125 mg**

Ampicillin as the trihydrate

**150 ml**

**Beecham**  
laboratories

**DIRECTIONS FOR MIXING:**  
Tap bottle until all powder flows freely. Add approximately 1/3 of the total amount of water for reconstitution (total = 100 ml) and shake vigorously to wet powder. Add the remainder of the water and again shake vigorously. Each 5 ml (1 teaspoonful) will contain Ampicillin Trihydrate equivalent to 125 mg. Ampicillin.

**USUAL DOSAGE:**  
Children: 250-500 mg/kg/day in divided doses every 6-8 hours.  
Adults: 250-500 mg every 6 hours.

**READ ACCOMPANYING INSERT BEFORE USE**  
6309/E

**KEEP TIGHTLY CLOSED** ● **SHAKE WELL BEFORE USING**  
Any unused portion of the reconstituted suspension must be discarded after 7 days at room temperature or 14 days under refrigeration.

Control No.

Exp. Date

Tear along perforation.

**BEECHAM LABORATORIES**  
DIV. OF BEECHAM  
INC., BRISTOL, TENN. 37620

**STORE DRY POWDER AT ROOM TEMPERATURE**

**CAUTION:** Federal law prohibits dispensing without prescription.

NDC 0029-6625-24

**TOTACILLIN®**  
ampicillin

for oral suspension

Equivalent to  
5.0 Gm Ampicillin

When reconstituted  
each 5 ml will contain

**125 mg**

Ampicillin as the trihydrate

200 ml

**Beecham**  
laboratories

**DIRECTIONS FOR MIXING:**

Tap bottle until all powder flows freely. Add approximately 1/3 of the total amount of water for reconstitution (total = 132 ml) and shake vigorously to wet powder. Add the remainder of the water and again shake vigorously. Each 5 ml (1 teaspoonful) will then contain Ampicillin Trihydrate equivalent to 125 mg Ampicillin.

**USUAL DOSAGE:**

Children: 50-100 mg/kg/day in divided doses every 6-8 hours.  
Adults: 250-500 mg every 6 hours.

**READ ACCOMPANYING INSERT BEFORE USE** 6447/D

**KEEP TIGHTLY CLOSED • SHAKE WELL BEFORE USING**  
Any unused portion of the reconstituted suspension must be discarded after 7 days at room temperature or 14 days under refrigeration.

Control No.

Exp. Date

See along perforation

**BEECHAM LABORATORIES**

Div. of BEECHAM INC. Bristol, PA 19003

**STORE DRY POWDER AT ROOM TEMPERATURE**

**CAUTION:** Federal law prohibits dispensing without prescription.

NDC 0029-6630-21  
**TOTACILLIN®**  
ampicillin  
for oral suspension

Equivalent to  
4.0 Gm. Ampicillin

When reconstituted,  
each 5 ml. will contain

**250 mg**

Ampicillin as the trihydrate

**80 ml**

**Beecham**  
laboratories

**DIRECTIONS: FOR MIXING:**  
Tap bottle until all powder flows freely. Add approximately 1/3 of the total amount of water for reconstitution (total = 53 ml) and shake vigorously to wet powder. Add the remainder of the water and again shake vigorously. Each 5 ml. (1 teaspoonful) will then contain Ampicillin Trihydrate equivalent to 250 mg.

**USUAL DOSAGE:**

Children: 50-100 mg/kg/day in divided doses every 6-8 hours.  
Adults: 250-500 mg every 6 hours.

**READ ACCOMPANYING INSERT BEFORE USE**

6312/D

**KEEP TIGHTLY CLOSED • SHAKE WELL BEFORE USING**  
Any unused portion of the reconstituted suspension must be discarded after 7 days at room temperature or 14 days under refrigeration.

Control No.  
Exp. Date

Tear along perforation.

**BEECHAM LABORATORIES**  
DIV. OF BEECHAM, INC. BRISTOL, TENN. 37620

**STORE DRY, POWDER AT ROOM TEMPERATURE**

**CAUTION:** Federal law prohibits dispensing without prescription.

NDC 0029-6630-23  
**TOTACILLIN®**  
ampicillin  
for oral suspension

Equivalent to  
5.0 Gm. Ampicillin  
When reconstituted  
each 5 ml will contain

**250 mg**

Ampicillin as the trihydrate

**100 ml**  
**Beecham**  
laboratories

**DIRECTIONS FOR MIXING:**  
Tap bottle until all powder flows freely. Add approximately 1/3 of the total amount of water for reconstitution (total = 66 ml) and shake vigorously to wet powder. Add the remainder of the water and again shake vigorously. Each 5 ml (1 teaspoonful) will contain Ampicillin Trihydrate equivalent to 250 mg Ampicillin.

**USUAL DOSAGE:**  
Children: 50-100 mg/kg/day in divided doses every 6-8 hours.  
Adults: 250-500 mg every 6 hours.

**READ ACCOMPANYING INSERT BEFORE USE**

64-48/D

KEEP TIGHTLY CLOSED. • SHAKE WELL BEFORE USING.  
Any unused portion of the reconstituted suspension must be  
discarded after 7 days at room temperature or 14 days under  
refrigeration.

Control No.

Exp. Date

See Dispensation

BEECHAM LABORATORIES  
DIV. OF BEECHAM INC. BRISTOL, TENN. 37620

STORE DRY POWDER AT ROOM TEMPERATURE  
CAUTION: Federal law prohibits dispensing without prescrip-  
tion.

NDC 0029-6630-22

**TOTACILLIN®**  
ampicillin  
for oral suspension

Equivalent to  
7.50 Gm. Ampicillin  
When reconstituted  
each 5 ml. will contain

**250 mg**

Ampicillin as the trihydrate

**150 ml**

**Beecham**  
laboratories

**DIRECTIONS FOR MIXING:**  
Place contents of bottle in glass or plastic container. Add approximately 1/3  
cup (80 ml) of water. Shake vigorously for 1 minute. Add the remainder of the  
water and shake vigorously to wet powder. Add the remainder of the  
water and again shake vigorously. Each 5 ml. (1 teaspoonful)  
will then contain Ampicillin Trihydrate equivalent to 250 mg.  
Ampicillin.

**USUAL DOSAGE:**  
Children: 50-100 mg/kg/day in divided doses every 6-8 hours.  
Adults: 250-500 mg every 6 hours.

**READ ACCOMPANYING INSERT BEFORE USE**  
6315/E

**KEEP TIGHTLY CLOSED** ● **SHAKE WELL BEFORE USING**  
Any unused portion of the reconstituted suspension must be discarded after 7 days at room temperature or 14 days under refrigeration.

Control No.

Exp. Date

Tear along perforation.

BEECHAM LABORATORIES

DIV. OF BEECHAM INC., BRISTOL, TENN. 37620

**STORE DRY POWDER AT ROOM TEMPERATURE**

**CAUTION:** Federal law prohibits dispensing without prescription.

NDC 0029-6630-24

**TOTACILLIN®**  
ampicillin  
for oral suspension

Equivalent to  
10.0 Gm Ampicillin

When reconstituted  
each 5 ml will contain

**250 mg**

Ampicillin as the trihydrate

**200 ml**

**Beecham**  
laboratories

**DIRECTIONS FOR MIXING:**

Tap bottle until all powder flows freely. Add approximately 1/3 of the total amount of water for reconstitution (total = 132 ml) and shake vigorously to wet powder. Add the remainder of the water and again shake vigorously. Each 5 ml (1 teaspoonful) will then contain Ampicillin Trihydrate equivalent to 250 mg Ampicillin.

**USUAL DOSAGE:**

Children: 50-100 mg/kg/day in divided doses every 6-8 hours.  
Adults: 250-500 mg every 6 hours.

6449/D

**READ ACCOMPANYING INSERT BEFORE USE**

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**Approval Package for:**

**APPLICATION NUMBER:**

**60-666 supplement**

Trade Names: Penbritin and Totacillin for Oral  
Suspension 125mg/5mL and  
250mg/5mL

Generic Name: ampicillin trihydrate

Sponsor: Beecham Laboratories

Approval Date: June 19, 1979

# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:**

**60-666 supplement**

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### Reviews / Information Included in this ANDA Review.

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Approval Letter(s)	X
Tentative Approval Letter(s)	
Final Printed Labeling	X
CSO Labeling Review(s)	
Medical Officer Review(s)	
Chemistry Review(s)	
Microbiology Review(s)	
Bioequivalence Review(s)	
Administrative Document(s)	
Correspondence	

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**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**APPROVAL LETTER**

**Beecham**  
laboratories

101 POSSUMTOWN ROAD, PISCATAWAY, NEW JERSEY 08854 - 201-469-5200

COPY 1

A-6

*OK to sign out  
JEB 6/19/79*

June 15, 1979

Food and Drug Administration  
Certifiable Drug Review Staff (HFD-53)  
Division of Generic Drug Monographs  
Bureau of Drugs  
5600 Fishers Lane  
Rockville, Maryland 20857

*6/19/79*  
*John D. Warner*  
For the Commissioner of Food and Drugs  
Food and Drug Administration  
Department of Health, Education and Welfare

Re: #60-666 (440.107c)

Gentlemen:

Reference is made to Beecham Laboratories' Approved Form 6 Antibiotic Application #60-666 covering Ampicillin for Oral Suspension. Additional reference is made to our approved supplement of February 8, 1979 which provided for a final printed Totacillin package insert reflecting a slight revision in the "Directions for Mixing" section.

At this time, we hereby supplement our Application to provide for a revised final printed package insert for the Penbritin brand of Ampicillin for Oral Suspension distributed by Ayerst Laboratories. This insert reflects a similar change in the "Directions for Mixing" section.

This supplement is submitted in triplicate, with two inserts in Copy 1 and one each in Copies 2 and 3.

Sincerely,

008497

BEECHAM LABORATORIES

*Robert E. Moore*

Robert E. Moore  
Associate Director  
Regulatory Affairs

RECEIVED  
JUN 18 1 43 PM '79  
FDA/BD/HFD-535

/ds

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**60-666 supplement**

**FINAL PRINTED LABELING**

# PENBRITIN\*

(ampicillin)

for  
ORAL SUSPENSION  
125 mg/5 ml  
and  
250 mg/5 ml

PEDIATRIC DROPS  
for  
ORAL SUSPENSION  
100 mg/ml

**CAUTION:** Federal law prohibits dispensing without prescription.

## DESCRIPTION

Chemical name: D(—)-alpha-aminobenzyl penicillin

PENBRITIN is an orally active, semisynthetic broad spectrum penicillin. It is inactivated by penicillinase.

## ACTIONS

### Microbiologic:

Ampicillin appears to act primarily by interfering with the synthesis or maintenance of the bacterial cell wall. It strongly inhibits the early lag and logarithmic phases of bacterial multiplication. In *in vitro* studies, ampicillin is bactericidal.

PENBRITIN is effective against the usual penicillin-susceptible gram-positive organisms, and in addition, many gram-negative pathogens. It is active *in vitro* against many strains of the following bacteria:

**GRAM-POSITIVE** — Alpha and beta hemolytic streptococci, nonpenicillinase-producing staphylococci, *Diplococcus pneumoniae*, *Clostridia* species, *Bacillus anthracis*, most strains of enterococci.

**GRAM-NEGATIVE** — *Haemophilus influenzae*, *Neisseria gonorrhoeae* and meningitidis, *Proteus mirabilis*, *Escherichia coli*, Salmonella (including *S. typhosa*), *Neisseria catarrhalis*, *Bacteroides funduliformis*, and Shigella.

All strains of *Pseudomonas* and most strains of *Klebsiella-Aerobacter* are resistant. Because ampicillin is destroyed by penicillinase, PENBRITIN is not effective against penicillinase-producing bacteria.

### Pharmacologic:

PENBRITIN is stable in acid and is therefore not destroyed by gastric juice. (Food, however, retards absorption.) PENBRITIN is well absorbed and produces high and persistent blood levels of unbound ampicillin. Ampicillin is the least protein bound of all the penicillins, averaging 20 percent as contrasted with 60 to 90 percent for the others. Blood serum levels of approximately 2 mcg/ml are achieved within one to two hours following a 250 mg oral dose to fasting adults. Detectable amounts persist in the blood for about six hours. There are high concentrations in the bile and urine. Ampicillin diffuses readily into most body tissues and fluids. However, penetration into the cerebral spinal fluid occurs only with meningeal inflammation. Ampicillin is excreted in the urine, largely unchanged, and this excretion can be delayed by concurrent administration of probenecid.

## INDICATIONS

PENBRITIN is indicated in the treatment of infections due to susceptible strains of the following:

**GRAM-NEGATIVE organisms:** Shigella, Salmonella (including *S. typhosa*), *H. influenzae*, *E. coli*, *P. mirabilis*, *N. gonorrhoeae*, and *N. meningitidis*.

**GRAM-POSITIVE organisms:** Streptococci, nonpenicillinase-producing staphylococci, and *D. pneumoniae*.

Bacteriologic studies to determine the causative organisms and their sensitivity to ampicillin should be performed. Because PENBRITIN is a broad spectrum antibiotic, therapy may be instituted prior to the results of sensitivity testing.

## CONTRAINDICATIONS

PENBRITIN is contraindicated in patients with a history of hypersensitivity to any penicillin.

## WARNINGS

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL THERAPY, IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. THESE REACTIONS ARE MORE APT TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR HYPERSENSITIVITY REACTIONS TO MULTIPLE ALLERGENS.

THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE THERAPY WITH A PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, AND OTHER ALLERGENS.

IF AN ALLERGIC REACTION OCCURS, THE DRUG SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE, OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

USAGE IN PREGNANCY: Safety for use in pregnancy has not been established.

## PRECAUTIONS

As with any antibiotic preparation, constant observation for signs of overgrowth of nonsusceptible organisms, including fungi, is essential. Should superinfection occur (usually involving *Aerobacter*, *Pseudomonas*, or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.

Periodic assessment of renal, hepatic, and hematopoietic function should be made during prolonged therapy. This is particularly important in prematures, neonates and other infants.

## ADVERSE REACTIONS

As with other penicillins, it may be expected that untoward reactions will be essentially limited to sensitivity phenomena. These are more likely to occur in individuals with a history of allergy, asthma, hay fever, or urticaria.

The following adverse reactions have been reported as associated with the use of ampicillin:

Gastrointestinal—glossitis, stomatitis, black "hairy" tongue, nausea, vomiting, enterocolitis, pseudomembranous colitis, and diarrhea. (These reactions are usually associated with oral administration.)

**PENBRITIN (ampicillin) for Oral Suspension & Pediatric Drops for Oral Suspension cont'd.**

Hypersensitivity reactions — erythematous maculopapular rashes have been reported fairly frequently; urticaria, erythema multiforme, and an occasional case of exfoliative dermatitis have been reported. Anaphylaxis is usually associated with parenteral administration.

Note: Urticaria, other skin rashes, and serum sickness-like reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, ampicillin should be discontinued unless, in the opinion of the physician, the condition being treated is life-threatening and amenable only to ampicillin therapy.

Hepatic — A moderate rise in serum glutamic oxaloacetic transaminase (SGOT) has been noted, particularly in infants. The significance of this finding is unknown.

Hemic and lymphatic — anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia, and agranulocytosis have been reported. These are usually reversible on discontinuation of the drug, and are believed to be hypersensitivity phenomena.

**DOSAGE AND ADMINISTRATION**

Infection	Usual Dosage* Adults	Usual Dosage* Children†
Respiratory tract	250 mg q 6 hours	50 mg/kg/day in equal doses q 6-8 hours
Gastrointestinal tract Genitourinary tract	500 mg q 6 hours	100 mg/kg/day in equal doses q 6-8 hours
Urethritis in Males or Females due to <i>N. gonorrhoeae</i>	3.5 g single oral dose administered simultaneously with 1.0 g of probenecid	
	In the treatment of complications of gonorrheal urethritis, such as prostatitis and epididymitis, prolonged and intensive therapy is recommended.	
	Cases of gonorrhea with a suspected primary lesion of syphilis should have dark-field examinations before receiving treatment. In all other cases where concomitant syphilis is suspected, monthly serologic tests should be made for a minimum of four months.	

\*Larger than usual dosages may be required for stubborn or severe infections. Smaller doses than those recommended above should not be used.

†The children's dosage is intended for individuals whose weight will not cause a dosage to be calculated greater than that recommended for adults. Children weighing more than 20 kg (44 lb) should be given the adult recommended dosage.

**PEDIATRIC DROPS:**

A suggested dosage regimen is:

Under 12 lb — 0.6 ml q 6 hours

12-25 lb — 1.0 ml q 6 hours

25-44 lb — 2.0 ml q 6 hours

**DURATION OF TREATMENT:** Medications should be continued for at least 48 to 72 hours after all symptoms have subsided or cultures have become negative. For any infection caused by hemolytic streptococci, at least 10 days of treatment is recommended to help prevent the occurrence of acute rheumatic fever or glomerulonephritis.

**DIRECTIONS FOR MIXING ORAL SUSPENSIONS**

Prepare suspensions at time of dispensing as follows: Tap bottle gently to loosen powder for ease of preparation. Add the required amount of water (see table below) in two portions—shake well after each addition of water. Each teaspoonful (5 ml) of reconstituted Oral Suspension will contain 125 mg or 250 mg ampicillin, depending upon the initial concentration. Each ml of reconstituted Pediatric Drops will contain 100 mg ampicillin.

Bottle Size	Amount of Water Required for Reconstitution
100 ml Oral Suspension	66 ml
200 ml Oral Suspension	132 ml
20 ml Pediatric Drops	11.5 ml

SHAKE WELL BEFORE USING.

**STABILITY**

**ORAL SUSPENSION:** No refrigeration required before mixing. After mixing, suspension may be kept at room temperature [21.1° C (70° F)] for 7 days or in a refrigerator [4.4° C (40° F)] for 14 days without significant loss of potency. KEEP TIGHTLY CLOSED.

**PEDIATRIC DROPS:** No refrigeration required before mixing. After mixing, suspension may be kept in a refrigerator for 14 days without significant loss of potency. KEEP TIGHTLY CLOSED.

**HOW SUPPLIED**

**PENBRITIN (ampicillin) for Oral Suspension — when reconstituted:**

Each 5 ml (one teaspoonful) contains 125 mg ampicillin as the trihydrate. Bottles for 100 ml (NDC 0046-0607-86) and 200 ml (NDC 0046-0607-82).

Each 5 ml (one teaspoonful) contains 250 mg ampicillin as the trihydrate. Bottles for 100 ml (NDC 0046-0611-86) and 200 ml (NDC 0046-0611-82).

**PENBRITIN (ampicillin) PEDIATRIC DROPS for Oral Suspension — when reconstituted:**

Each ml contains 100 mg ampicillin as the trihydrate. Bottles for 20 ml (NDC 0046-0625-20).

Distributed by  
**AYERST LABORATORIES INCORPORATED**  
New York, N.Y. 10017