CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 61-621

Name: Erythromycin Tablets

Sponsor: Abbott Laboratories

Approval Date: July 11, 1972

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 61-621

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 61-621

APPROVAL LETTER

BD-145

July 11, 1972

Our reference:
61-621 (148e.26)

Hartley C. Ericson
Corporate Regulatory Operations
ABBOTT LABORATORIES
North Chicago, Illinois 60064

Dear Mr. Ericson:

Enclosed for your files is an approved copy of the Antibiotic Form 6 application submitted March 20, 1972, to provide for the certification of batches of erythromycin tablets manufactured at your facilities in North Chicago.

Abbott Laboratories is in a position to request certification for batches of erythromycin tablets which have been manufactured in accordance with the procedures outlined in the Form 6. An expiration date of 24 months may be used for this product. As additional stability data become available they should be submitted for inclusion in the Form 6 file.

The information in the Antibiotic Form 6 should be kept up-to-date by submitting amendments whenever changes occur in the manufacturing facilities, operating procedures, batch size, quality control tests, labeling, supervisory personnel, etc.

Approval of your Form 6 was supported by data from two single dose and one multiple dose blood level studies. Since the tablets used in all of these studies were from a single batch of tablets produced in your pilot plant, we believe it would be prudent to conduct a multiple dose study using tablets from one of your first production-size batches. The data from this additional study should be submitted for inclusion in the Form 6 file.

Please be reminded of the regulations set forth in §146.14 of the antibiotic regulations requiring you to establish and maintain certain records and reports concerning the experience with each antibiotic drug product. Since ERYTHROMYCIN BASE FILMTAB TABLETS

is a new product for your company, such reports are due every three (3) months during the first year.

Sincerely yours,

John D. Harrison
Certifiable Drug Review Staff (BD-145)
Division of Anti-Infective Drug Products

Enclosure

cc:
CHI-DO
BD-145
BD-145/OD
BD-430/lab.
JDHarrison:hb

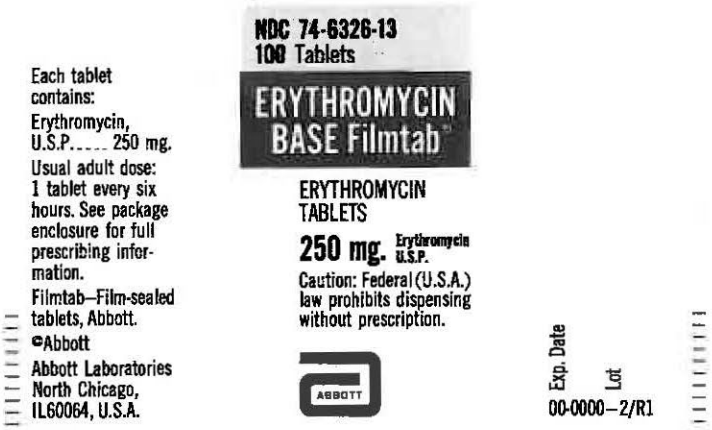
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 61-621

LABELING

6. Each copy of the application shall contain a copy of each label and all other labeling to be used for the drug.



ERYTHROMYCIN BASE Filmtab®

ERYTHROMYCIN TABLETS

ABBOTT

ERYTHROMYCIN BASE
Filmtab®
ERYTHROMYCIN TABLETS

DESCRIPTION

Erythromycin is produced by a strain of *Streptomyces erythraeus* and belongs to the macrolide group of antibiotics. It is basic and readily forms salts with acids. The base, the stearate salt, and the esters are poorly soluble in water, and are suitable for oral administration.

ERYTHROMYCIN BASE Filmtab tablets contain erythromycin, U.S.P. base in a unique, non-enteric film coating.

ACTIONS

The mode of action of erythromycin is by inhibition of protein synthesis without affecting nucleic acid synthesis. Resistance to erythromycin of some strains of *Haemophilus influenzae* and staphylococci has been demonstrated. Culture and susceptibility testing should be done. If the Kirby-Bauer method of disc susceptibility is used, a 15 mcg. erythromycin disc should give a zone diameter of at least 18 mm. when tested against an erythromycin susceptible organism.

Orally administered erythromycin is readily absorbed by most patients, especially on an empty stomach, but patient variation is observed. Due to its formulation and non-enteric coating, this erythromycin tablet gives reliable blood levels in

®FILMTAB — Film-sealed tablets, Abbott.

the average subject; however, the levels may vary with the individual.

After absorption, erythromycin diffuses readily into most body fluids. In the absence of meningeal inflammation low concentrations are normally achieved in the spinal fluid, but passage of the drug across the blood-brain barrier increases in meningitis. In the presence of normal hepatic function, erythromycin is concentrated in the liver and excreted in the bile; the effect of hepatic dysfunction on excretion of erythromycin by the liver into the bile is not known. After oral administration, less than 5 percent of the activity of the administered dose can be recovered in the urine.

Erythromycin crosses the placental barrier but fetal plasma levels are generally low.

INDICATIONS

Streptococcus pyogenes (Group A beta hemolytic streptococcus) : Upper and lower respiratory tract, skin, and soft tissue infections of mild to moderate severity.

Injectable benzathine penicillin G is considered by the American Heart Association to be the drug of choice in the treatment and prevention of streptococcal pharyngitis and in long-term prophylaxis of rheumatic fever.

When oral medication is preferred for treatment of the above conditions, penicillin G, V, phenoxymethyl penicillin, or erythromycin are alternate drugs of choice.

When oral medication is given, the importance of strict adherence by the patient to the prescribed dosage regimen must be

stressed. A therapeutic dose should be administered for at least 10 days.

Alpha-hemolytic streptococci (viridans group): Short-term prophylaxis of bacterial endocarditis prior to dental or other operative procedures in patients with a history of rheumatic fever or congenital heart disease who are hypersensitive to penicillin. (Erythromycin is not suitable prior to genitourinary surgery where the organisms likely to lead to bacteremia are gram-negative bacilli or the enterococcus group of streptococci.)

Staphylococcus aureus: Acute infections of skin and soft tissue of mild to moderate severity. Resistant organisms may emerge during treatment.

Diplococcus pneumoniae: Upper respiratory tract infections (e.g. otitis media, pharyngitis) and lower respiratory tract infections (e.g. pneumonia) of mild to moderate degree.

Mycoplasma pneumoniae (Eaton agent, PPLO): In the treatment of primary atypical pneumonia, when due to this organism.

Treponema pallidum: Erythromycin is an alternate choice of treatment for primary syphilis in patients allergic to the penicillins. In treatment of primary syphilis, spinal fluid examinations should be done before treatment and as part of follow-up after therapy.

Corynebacterium diphtheriae and *C. minutissimum:* As an adjunct to antitoxin, to prevent establishment of carriers, and to eradicate the organism in carriers.

In the treatment of erythrasma.

Entamoeba histolytica: In the treatment of intestinal amebiasis only. Extraenteric amebiasis requires treatment with other agents.

Listeria monocytogenes: Infections due to this organism.

Based on a review of this drug by the National Academy of Sciences – National Research Council and/or other information, FDA has classified the other indications as follows:

"Probably" effective: *Neisseria gonorrhoeae:* Erythrocin (erythromycin) is an alternate choice of treatment for gonorrhea in patients allergic to the penicillins. Before treatment of gonorrhea, patients who are suspected of also having syphilis should have a microscopic examination for T. pallidum (by immunofluorescence or darkfield) before receiving erythromycin, and monthly serologic tests for a minimum of 4 months.

"Possibly" effective: *Hemophilus influenzae:* For upper and lower respiratory tract infections of mild to moderate severity. Not all strains of this organism are susceptible at the concentrations ordinarily achieved.

Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS

Erythromycin is contraindicated in patients with known hypersensitivity to this antibiotic.

WARNINGS

Usage in pregnancy: Safety for use in pregnancy has not been established.

PRECAUTIONS

Erythromycin is principally excreted by the liver. Caution should be exercised in administering the antibiotic to patients with impaired hepatic function.

Surgical procedures should be performed when indicated.

ADVERSE REACTIONS

The most frequent side effects of oral erythromycin preparations are gastrointestinal, such as abdominal cramping and discomfort, and are dose-related. Nausea, vomiting, and diarrhea occur infrequently with usual oral doses.

During prolonged or repeated therapy, there is a possibility of overgrowth of nonsusceptible bacteria or fungi. If such infections occur, the drug should be discontinued and appropriate therapy instituted.

Mild allergic reactions such as urticaria and other skin rashes have occurred. Serious allergic reactions, including anaphylaxis, have been reported.

DOSAGE AND ADMINISTRATION

Optimum blood levels are obtained when doses are given on an empty stomach.

Adults: 250 mg. every six hours is the usual dose. Dosage may be increased up to 4 or more grams per day according to the severity of the infection.

Children: Age, weight, and severity of the infection are important factors in determining the proper dosage. 30-50 mg./kg./day, in divided doses, is the usual dose. For more severe infections this dose may be doubled.

If dosage is desired on a twice-a-day schedule in either adults or children, one-half of the total daily dose may be given every 12 hours, one hour before meals.

In the treatment of streptococcal infections, a therapeutic dosage of erythromycin should be administered for at least 10 days. In continuous *prophylaxis* of streptococcal infections in persons with a history of rheumatic heart disease, the dose is 250 mg. twice a day.

When used prior to surgery to prevent endocarditis (see *Alpha-hemolytic streptococci*), a recommended schedule for adults is: 500 mg. before the procedure and 250 mg. every 6 hours for 4 doses after the procedure. For small children: 30 to 50 mg./kg./day divided into three or four evenly spaced doses.

For treatment of primary syphilis: 30-40 grams given in divided doses over a period of 10-15 days.

For treatment of gonorrhea: 500 mg. four times daily for 5 days.

For intestinal amebiasis: Adults: 250 mg. four times daily for 10 to 14 days. Children: 30-50 mg./kg./day in divided doses for 10 to 14 days.

HOW SUPPLIED

ERYTHROMYCIN BASE Filmtab (erythromycin tablets) is supplied as:

Erythromycin 250 mg., pink, capsule-shaped tablets in bottles of 100, NDC-74-6326-13.

ABBOTT LABORATORIES
NORTH CHICAGO, IL60064
00-0000/R1—000—FEB., 1972 PRINTED IN U.S.A.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 61-621

CHEMISTRY REVIEWS

CHEMISTRY REVIEW NOTES
May 25, 1972

RE: Erythromycin (base)
Tablets, Form 6, #61-621
submitted by Abbott Labs,
March 20, 1972

The manufacturer submitted a complete list of ingredients used in the manufacture of the dosage form.

The erythromycin base met the requirements of CFR 21-148e.1 and also conform to the USP XVIII monograph. The other raw ingredients all conform to USP XVIII standards.

The finished product met the requirements for certification as set forth in CFR 21-148e.26. Although not required for certification, an identity test on the finished product would be desirable.

The results for the disintegration time for these samples compare favorably with those of the Upjohn tablets.

Results for disintegration time and moisture follow:

	Disintegration time	Moisture
Lot No. 4269-047A M5246	Ok (Abbott) Ok (our Lab)	(b) (4)% (Abbott) (b) (4)% (Our Lab)
Limits:	disintegrates within one hour	not more than 7.5%
Lot No. 4269 -046 M5247	Ok (Abbott) Ok (Our Lab)	(b) (4)% (Abbott) % (Our Lab)
Limits:	disintegrates within one hour	not more than 7.5%
Lot No. 4269-017 M5248	Ok (Abbott) Ok (Our Lab)	(b) (4)% (Abbott) (b) (4)% (Our Lab)
Limits:	disintegrates within one hour.	not more than 7.5%

Jocelyn G. Blakely

Jocelyn G. Blakely
Research Chemist, ACB

ANALYTICAL RESULTS FOR ERYTHROMYCIN BASE FILMTAB TABLETS, 250 MG.

REPRESENTATIVE SAMPLES MADE BY PROPOSED FORMULA

Lot No. 4269-047 A: M5246

Antibiotic Used: Code 27915, Erythromycin, U.S.P., Base, Lot No. 08-314-CD.

Analytical Results:

Erythromycin [(b)(4)] mg. per tablet; [(b)(4)]% of label claim

Moisture [(b)(4)]%

Disintegration Time 6 tablets disintegrate within [(b)(4)] minutes

Lot No. 4269-046: M5247

Antibiotic Used: Code 27915, Erythromycin, U.S.P., Base, Lot No. 08-314-CD.

Analytical Results:

Erythromycin [(b)(4)] mg. per tablet; [(b)(4)]% of label claim

Moisture [(b)(4)]%

Disintegration Time 6 tablets disintegrate within [(b)(4)] minutes

Lot No. 4269-017: M5248

Antibiotic Used: Code 27915, Erythromycin, U.S.P., Base, Lot No. 854-9491.

Analytical Results:

Erythromycin [(b)(4)] mg. per tablet; [(b)(4)]% of label claim

Moisture [(b)(4)]%

Disintegration Time 6 tablets disintegrate within [(b)(4)] minutes

ABBOTT LABORATORIES
Quality Assurance Administrative Services, PPD
April 3, 1972

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 61-621

MICROBIOLOGY REVIEWS

MICROBIOLOGIST'S REVIEW
BLOOD LEVEL STUDIES

Form 6 #_____
Abbott Laboratories
Erythromycin Base Film tabs, 250 mg

Two single dose blood level studies and one multiple dose study were performed on Abbott formulation [redacted] (b) (4), Lot #12-188-AR.
Reference - Upjohn E-mycin -

Single Dose Study
Lot #062AK11
Multiple Dose Study
Lot #1GA80F0

The two single dose studies were done in-house. The multiple dose study was under the direction of [redacted] (b) (4)
Crossover studies were performed using 24 subjects, 12 in each group.

Studies were performed in accordance with FDA Guidelines.

The single dose study showing the less comparable and/or lower blood levels was chosen for inclusion in the statistical analysis.

Assay

Abbott	109% of label claim
Upjohn	98% of label claim

The lot of Abbott erythromycin base tablets was made on pilot plant equipment and was a [redacted] (b) (4) tablet lot.

Disintegration times

Abbott - Simulated gastric fluid

Tablet No.	-	Time
1.		[redacted] (b) (4)
2.		
3.		
4.		
5.		
6.		
7.		
8.		
9.		
10.		
11.		
12.		

Time
Av. 44.92 min.

E mycin - Gastric - Intestinal

Tablet No.	-	Time (b) (4)
1.		
2.		
3.		
4.		
5.		
6.		
7.		
8.		
9.		
10.		
11.		
12.		

Time
Av. 69.66 min.

The following mean blood serum levels were obtained.

Single Dose Study

Hours	.75	1.5	2	3	4.5	6	8	12
Abbott	.06723	.31396	.47046	.82391	.38314	.19678	.09664	.01914
Upjohn	0	0	.04909	1.23418	.65987	.30209	.14691	.03973

Statistical Analysis

1. An F test of the null hypothesis H_0 : Direct drug effects plus carryover drug effects = 0 for all time points of the curve, gave the results
   F(8, 13) = 2.45436

   This value is not in a highly significant range indicating that over the points examined on the blood level curve, the points are generally comparable.

2. A t-test of the null hypothesis H_0 : that the area under the difference curves = 0 which is the same as a test for equal areas for the two drugs.

   t-statistic (20 df H_0) is
   -1.47801
   The - value indicates a value in favor of the Upjohn product. However, the value is not significant indicating that the areas are equal.

3. T-tests on all individual time values selecting the peak value (3 hours).

   t-statistic (univariate) with 20 df
   -1.32833
   This value favors Upjohn but is not in a highly significant range.

4. The 95% simultaneous confidence intervals around zero showed that zero was included at all time points showing no seriously divergent values.

Multiple Dose Study

The following mean blood levels were obtained.

Hours	1	1.5	2	3	4.5	6	8	9
Abbott	.04218	.27696	.57627	1.15364	.66714	.35764	.78287	.78409
Upjohn	0	0	.01368	1.12469	.85755	.50041	.83551	1.11169

Hours	48	49.5	50.0	51	52.5	54	55.5
Abbott	.71651	1.8415	2.69437	2.01282	1.17787	.69368	1.69387
Upjohn	.98734	.88182	1.49083	1.98337	1.27759	.78391	.99600

Hours	57	58.5	60
Abbott	1.52555	.88064	.49968
Upjohn	1.29037	.85546	.53537

Statistical Analysis
0-9 hours

1. An F test of the null hypothesis, H_0 : direct drug effects plus carryover drug effects = 0 for all time points of the curve, gave the results
   F (8, 13) = 5.17927

   The result is significant indicating a difference in the overall curve in favor of Abbott.

2. A t-test of the null hypothesis, H_0 = that the area under the difference curve = 0 which is the same as a test for equal areas for the two drugs.

   t-statistic (20 df $\sim H_0$) is
   -.152276

   The value of the t-statistic is not in a range to be significant at all.

3. t-test on all individual time values, selecting the peak value test. (3 hour)

   t-statistic = .101748

   However the t-statistic at 2-hour is equal to 4.1852 which is in a range to be slightly significant.

4. The calculation of the 95% simultaneous confidence intervals around zero showed that zero was included in all cases.

Multiple Dose Study
48-60 hours

1. An F test of the null hypothesis, H_0 : direct drug effects plus carryover drug effects = 0 for all time points of the curve gave the result
F (10, 11) = 3.06351

   The result is not in a range to be significant indicating similarity over all time points for both curves.

2. A t-test of the null hypothesis, H_0 : that the area under the difference curve = 0 which is the same as a test for equal areas for the two drugs
t-statistic (20 df H_0) is
1.77483

   This is not in a range to be significant thus indicating equal areas.

3. t-test on all individual time values selecting the peak value test (50-51 hours)

   At 50 hours, the t-statistic is
3.17533

   This value is border-line with regard to significance. The value would be in favor of Abbott.

   At 51 hours, the t-statistic is .11994 which is not in a range to be significant.

4. The calculation of the 95% simultaneous confidence intervals around zero include zero in all cases showing no seriously divergent values.

Conclusions

1. There is no reference product of this type on the market.

2. All blood level studies were conducted on one lot (pilot plant equipment).

3. The blood level curves with the Abbott base tablets were comparable to E-mycin (Upjohn) reference curves.

Recommendations

1. The blood level studies are approvable and show comparability with the reference product.

2. Since this is a new product, for which we have no information, an additional multiple dose blood level study should be performed on a larger production batch.

Orig F6 dup F6 (145) BD-100
BD-140 BD-401 BD-140/MO
BD-140/Norton BD-140/MKBruch:rg

Mary K. Bruch
Mary Bruch

Acard. Smith 7/11/72

MICROBIOLOGICAL ASSAY REVIEW NOTES
May 22, 1972

Re: Erythromycin (base) Tablets
Form 6 - #61-621
Submitted by Abbott Labs
March 20, 1972

Please see the review submitted for Form 5 #50-297, Abbott erythro. ethyl succinate chewable tablets, May 19, 1972. The comments in that review apply to this submission also, since exactly the same procedures are described in both submissions.

Three lots of exhibit samples were assayed according to instructions in 21 CFR 148e.26(b)(1) and the results follow:

Lot # 4269-047A (M5246)

	Day 1		Day 2
P1	(b) (4)	P3	(b) (4)
2		4	

average = 260 mg/tab

Lot #4269-046 (M5247)

	Day 1		Day 2
P1	(b) (4)	P3	(b) (4)
2		4	

average = 263 mg/tab

Lot # 4269-017 (M5248)

	Day 1		Day 2
P1	(b) (4)	P3	(b) (4)
2		4	

average = 274 mg/tab

These samples meet potency requirements, and these results compare very well to the usual results obtained from assays of Upjohn's tablets.

Elsie Tarcza

Elsie Tarcza
Microbiological Assay Branch
National Center for Antibiotics Analysis

ANTIBIOTIC RESIDUE REVIEW NOTES
May 22, 1972

Re: Erythromycin (base) Tablets
Form 6 - #61-621
Submitted by Abbott Labs.
March 20, 1972

The following three lots of exhibit samples #4269-047A (M5246), #4269-046 (M5247), and #4269-017 (M5248) were assayed for penicillin contamination.

No detectable penicillin was found.

Henry H. Bryant
Antibiotic Residue Branch
National Center for Antibiotics Analysis

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 61-621

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

: Mr. Harrison - BD-145

DATE: May 26, 1972

FROM : B. Arret, Acting Deputy Director, NCAA - BD-145

SUBJECT: ERYTHROMYCIN BASE TABLETS - ABBOTT LABS - Form 6 - #61-621

The application has been reviewed and comments from the laboratories are attached. The critical comments are:

1. Our memorandum of April 13, 1972 stated that the [redacted] (b) (4) assay for erythromycin was unacceptable.

2. The tenplate used for the plate assay requires that the volume of solution added to the cups be measured.

B. Arret

cc:
Dr. Wright - BD-400
Mr. Arret
Mrs. Tarcza
Mrs. Blakely
Mr. Bryant
Mr. Selzer
DA Lab

No attachment was located with the original records

BArret:bhp

MEMO RECORD	AVOID ERRORS PUT IT IN WRITING	DATE 4-5-72
FROM: John D. Harrison (BD-145)		OFFICE
TO: Mr. Bernard Arret (BD-430)		DIVISION
SUBJECT: ABBOTT LABS — Erythromycin (Base) Tablets, 250 mg		

SUMMARY

§ 148e.26 Form 6 of 6-621

Abbott Labs. proposes to report certification for batches of erythromycin tablets produced as described in attached Form 6 application. Exhibit samples from 3 batches have been presented — please evaluate.

SIGNATURE John R. Harrison

DOCUMENT NUMBER 5022

FORM FDH-2034 (11/66)

March 29, 1972

Our reference:
61-621 (148e.26)

Mr. Hartley C. Ericson
Director, Corporate Regulatory
Operations
ABBOTT LABORATORIES
North Chicago, Illinois 60064

Dear Mr. Ericson:

We acknowledge receipt of your Antibiotic Form 6 application dated March 20, 1972, to provide for the certification of batches of ERYTHROMYCIN BASE FILMTAB TABLETS, 250 mg.

We have established a numerical identification system for our Form 6 files and have assigned number 61-621 to this application. All future correspondence pertaining to this Form 6 should refer to this number and to the antibiotic regulation - §148e.26 - under which batches of the drug are eligible for certification.

We would like to examine exhibit samples from three batches of the proposed new product. Please submit not less than 30 tablets from each exhibit batch.

Sincerely yours,

John D. Harrison
Certifieble Drug Review Staff (BD-145)
Division of Anti-Infective Drug Products

cc:
BD-145
BD-145/OD
BD-430/lab.
JDHarrison:hb

MEMO RECORD	AVOID ERRORS PUT IT IN WRITING	DATE 3-28-72
FROM: John D. Harrison (BD-145)		OFFICE
TO: Mr. Robert Norton (BD-140)		DIVISION
SUBJECT: Abbott Labs - Erythromycin (base) Tablets, 250mg.		

SUMMARY

21 CFR 314.8(a) (6) Form 4 61-621

Abbott Labs. proposes to market certain for tablets of erythromycin base tablets. Please evaluate their bio data & attached application. (A duplicate copy is also attached for your file.)

SIGNATURE John D. Harrison (BD-145)	DOCUMENT NUMBER 7022

FORM FDH-2034 (11/66)