

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 020357, S010

Trade Name: GLUCOPHAGE TABLETS

Generic Name: METFORMIN HYDROCHLORIDE

Sponsor: BRISTOL-MYERS SQUIBB

Approval Date: 10/22/98

**Indication(s): PROVIDES FOR THE NEW COMBINATION USE
OF METFORMIN AND INSULIN IN TYPE 2 DIABETES**

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APPLICATION: 020357, S010

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	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tentative Approval Letter				X
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Final Printed Labeling		X		
Medical Review(s)	X			
Chemistry Review(s)	X			
EA/FONSI	X			
Pharmacology Review(s)				X
Statistical Review(s)	X			
Microbiology Review(s)				X
Clinical Pharmacology				X
Biopharmaceutics Review(s)				
Bioequivalence Review(s)				X
Administrative Document(s)/ Correspondence	X			

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 020357, S010

APPROVAL LETTER

NDA 20-357/S-010

Bristol-Myers Squibb
Attention: Mr. Warren C. Randolph
Director, U.S. Regulatory Liaison
P.O. Box 4000
Princeton, NY 08543-4000

Dear Mr. Randolph:

Please refer to your supplemental new drug application (NDA) dated April 23, 1998, received April 23, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Glucophage® (metformin hydrochloride) Tablets, 500 mg, 750 mg, 850 mg, and 1000 mg.

We acknowledge receipt of your submissions dated April 30, July 1, 15, 16, and October 21, 1998.

This supplemental new drug application provides for the new combination use of metformin and insulin in type 2 diabetes.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted October 21, 1998). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplemental NDA 20-357/S-010." Approval of this submission by FDA is not required before the labeling is used.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

**APPEARS THIS WAY
ON ORIGINAL**

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Ms. Jena Weber, Project Manager, at (301) 827-6422.

Sincerely,

/S/

Solomon Sobel, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

**APPEARS THIS WAY
ON ORIGINAL**

FINAL PRINTED LABELING HAS NOT BEEN SUBMITTED TO THE FDA.

DRAFT LABELING IS NO LONGER BEING SUPPLIED SO AS TO ENSURE ONLY CORRECT AND CURRENT INFORMATION IS DISSEMINATED TO THE PUBLIC.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020357, S010

MEDICAL REVIEW(S)

NDA 20357
Sponsor: Bristol-Myers Squibb
Drug: Glucophage (metformin)

Received: 7/10/98
Reviewed: 8/17/98
Doct: N20537S

SE-10

MEDICAL OFFICER'S REVIEW OF SUPPLEMENTAL NDA APPLICATION

GENERAL INFORMATION

The submission requests approval of a revised labeling for the concomitant use of metformin with insulin in type 2 diabetes.

In support of this request, Sponsor has provided data derived from two clinical trials in which the concomitant use of metformin with insulin improved glycemic control over that achieved with insulin alone, or maintained glycemic control with reduced insulin dosing.

In addition, Sponsor cites a number of published reports where the use of metformin and insulin in type 2 diabetes has been studied, to presumably arrive at the same general conclusions than those derived by the Sponsor's own clinical trials. The Sponsor has provided a rather thorough analysis of the results of such published trials.

The Sponsor refers to the recent approval of the concomitant use of troglitazone and insulin, to state that the superiority of the concomitant use of metformin and insulin is predicated on the following two observations:

1. The troglitazone+insulin combination results in an increase in body weight and LDL-cholesterol values; whilst the metformin+insulin combination stabilizes or decreases such unwelcome parameters affecting the cardiovascular outcome of diabetic patients; and,
2. The troglitazone+insulin combination has liver toxicities not present in the metformin+insulin combination.

On that basis, Sponsor is requesting Priority Application status. This Medical Officer agrees with the granting of such status.

BIOEQUIVALENCY STUDIES

None needed. None submitted.

CHEMISTRY AND MANUFACTURING

None needed. None submitted.

PHARMACOTOXICOLOGY

None needed. None provided.

CLINICAL STUDIES

Generalities

There were some 105 patients randomized during the two well-controlled clinical trials, with some 52 treated with the metformin+insulin combination.

Study CV138-016

This was a randomized, double-blind, placebo-controlled parallel study of type 2 diabetic patients initially on relatively high doses of daily insulin. Subjects were randomized to receive insulin+metformin versus insulin+placebo. Thus, the crucial arm of metformin+placebo is missing with the consequence that synergism (very likely to exist) cannot however be proven.

Objective of the study: evaluate the effectiveness of the metformin+insulin combination versus the insulin alone combination, with particular emphasis on the further correction of hyperglycemia.

Subjects had, at entry, mean HbA1c levels of greater than 9%. The normal for the used test was equal or less than 5.8%. They were treated for 24 weeks. They were receiving more than 50 units of insulin per day, at entry. Randomized patients followed a titration schedule during which the dosage of metformin was increased to a maximal dose, from 500 mg to 2500 mg/d.

Efficacy end-points: glycated hemoglobins, fasting glucose, daily insulin dose, body weight and lipid profile; with particular emphasis on change in glycemic control.

Efficacy results: During the 6 month period of treatment, HbA1c levels decreased significantly for the metformin+insulin combination, when compared to the insulin+placebo combination. At the end of the trial, HbA1c values decreased by 2.6% for the metformin+insulin combination, as opposed to a 1.6% decrease in the insulin alone group. Thus, the added improvement of HbA1c values due to metformin is 1.0% units -- a clinically highly significant improvement, particularly since the daily insulin dosage showed a reduction in the metformin+insulin group of -2.8 units/d, as opposed to an increase of 26.3 units/day in the insulin alone group.

Total clinical significance rests on the following simultaneous changes in the metformin+insulin treatment versus the insulin alone treatment groups: HbA1c values were significantly reduced (statistical as well as clinical) while the daily insulin dosing was significantly reduced (thus improving hyperinsulinemia, a suspected risk factor among type 2 diabetics). There was no change in the body weight between the treated groups, indicating that greater glycemic control didn't result in an increase in body weight, that could only occur if more insulin was administered to achieve better glycemic control.

As predictable from the small group of studied patients, no new safety issue was uncovered during this study. No deaths were reported during the study. No abnormal laboratory values surfaced during the study.

The Sponsor concludes: "These data demonstrate that metformin effectively and safely improves blood glucose control in patients with poorly controlled insulin-treated NIDDM." This Medical Officer concurs with that assessment.

Study CV138-020

This, also, is a randomized, double-blind, placebo-controlled parallel study of type 2 diabetic patients initially on relatively high doses of insulin. Subjects were randomized to receive insulin+metformin versus insulin+placebo. Again, the crucial arm of metformin+placebo is missing with the consequence that synergism (very likely to exist) cannot however be proven.

Objective of the study: evaluate the effectiveness of the metformin+insulin combination versus the insulin alone combination, when a standard regimen of insulin was administered to both groups.

Subjects had, at entry, mean HbA1c levels of less than 7.5%. The normal for the used test was equal or less than 5.8%. Some 20 patients were treated for 13 weeks. They were given from 500 mg to 4500 mg/d of metformin. The dose of insulin was adjusted up or down, according to predetermined clinical parameters in order to maintain the desired glucose control.

Efficacy end-points: glycated hemoglobins, fasting blood glucose (FBG), total daily insulin dose, lipid profile and body weight.

At the end of the trial, HbA1c values showed a greater mean decrease from baseline in the metformin+insulin group compared to the insulin+placebo group (-0.7% versus -0.0%), FBG followed the same pattern (-22.4 mg/dL versus +24.3 mg/dL), total daily insulin was decreased by 22.2 units versus 1.0 units, LDL-cholesterol decreased by -25 mg/dL versus -6 mg/dL, and body weight decreased by 3 lbs versus an increase of 1 lb in the insulin alone group. In addition systolic as well as diastolic BP were improved by the combination therapy versus the insulin alone therapy. No new safety issues were uncovered during this relatively small study which, in addition, didn't last long enough to permit a conclusive reevaluation of safety. But the safety of metformin has been evaluated independently during long-term previous studies as continued to be studied in on-going long-term studies. On the other hand, this Medical Officer cannot conclusively state that, on the basis of the submitted data, the combination would not affect the frequency of hypoglycemia in treated subjects.

The Sponsor concludes: "These data demonstrate that metformin effectively and safely reduced the amount of insulin required to control blood glucose in patients with insulin-resistant type 2 diabetes." This Medical Officer doesn't agree with the characterization of patients as insulin-resistant diabetics, but agrees with all the other conclusions of the Sponsor; essentially, that the combination improves a number of key clinically significant parameters.

Published Clinical Reports

Some nineteen (19) publications are submitted and discussed, concerning a total of 929 treated patients with type 2 diabetes, more than 550 of whom were treated with the metformin+insulin combination.

These publications generally support the above conclusions without bringing anything new to the general picture provided by the two well-controlled trials. However, since the number of studied patients, the well-controlled nature of some studies, as well as the seemingly rigorous methodological approach in many of these studies, can only strengthen the general picture of safety and effectiveness. Some of the references also address safety points, e.g., the circulating lactate issue.

Several publications do present some visible flaws, e.g., studies during which treatment period was too short to appreciate the full efficacy of the combination treatment.

LABELING REVIEW

The labeling changes mainly concern the introduction, in the labeling, of the results obtained by the novel well-controlled studies. Likewise, the indication section has been appropriately revised.

In the Warning section, the labelling should state that when transferring patient from insulin alone to the metformin+insulin combination, careful retitration should be instituted in order to obtain the best achievable glycemic control without running the risk of increasing the frequency of hypoglycemic episodes.

RECOMMENDED REGULATORY ACTION

The submission is approvable, provided that the suggested modifications to the labeling are accepted by the Sponsor.

/S/

**APPEARS THIS WAY
ON ORIGINAL**

John L. Gueriguian
Medical Officer
8/17/98

/S/

cc.
The File
Dr. Fleming
Dr. Gueriguian

8/24/98

**APPEARS THIS WAY
ON ORIGINAL**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020357, S010

CHEMISTRY REVIEW(S)

DF
AUG 12 1998

CHEMIST'S REVIEW		
Organization CDER/HFD-510 Division of Metabolism and Endocrine Drug Products	NDA # 20-357 Approved: 29-DEC-1994	
Name and Address of Applicant: Bristol-Myers Squibb Pharmaceutical Research Institute Princeton, NJ 08543-400 P.O. Box 4000 (609) 252-4000 (609) 252-4732	Supplement SE1-010 Doc. 23-APR-1998 Rec. 23-APR-1998	
	Name Of The Drug Glucophage Tablets	
	Nonproprietary Name Metformin Hydrochloride Tablets	
Supplement provides for the use of Glucophage with insulin.	Amendment(s) SE1-010 BC Doc 30-APR-1998 Rec 06-MAY-1998	
Pharmacological Category Antihyperglycemic Agent	How Dispensed Oral Rx	Supporting Documents --
Dosage Form Tablets	Potencies 500, 625, 750, 850 and 1000 mg	
Chemical Name and Structure $C_4H_{11}N_5 \cdot HCl$ MW = 129.17 + 36.46 = 165.63 CAS 657-24-9 (base) 1115-70-4 (hydrochloride) <div style="text-align: center; margin: 10px 0;"> </div> <i>N,N</i> -Dimethylbiguanide hydrochloride or <i>N,N</i> -Dimethylimidodicarbonimidic diamide monohydrochloride		
Comments: Neither the drug substance, metformin HCl, nor the drug product, Glucophage (metformin HCl) Tablets, have been modified. The 30-APR-1998 supplement amendment provides for the Environmental Assessment Report (EAR) associated with the 23-APR-1998 Supplement. Accordingly to this EAR the Expected Introduction Concentration (EIC) and the Expected Environmental Concentration (EEC) values are _____ respectively. There is a margin of at least _____ fold between the predicted EEC and the minimum inhibitory concentrations (_____ microbial inhibition data), the no observed effect concentration (NOEC _____ aquatic toxicity based on data from [the aquatic specie] <i>Daphnia magna</i>) or EC50 (median effective concentration relative to immobilization of <i>Daphnia</i> is _____). Therefore, the projected increase in the volumes of metformin will not pose a significant risk of harm to aquatic organisms or to the microorganisms at existing publicly owned treatment works (POTWs). All this data is summarized in the data table of the Nonconfidential Appendix of the submission		
Conclusions and Recommendation Satisfactory CMC information has been provided to support the use of Glucophage (Metformin HCl) Tablets with Insulin. From the chemistry point of view, this supplement can be approved.		
Date Completed: 12-AUG-1998 <div style="text-align: right; margin-top: 10px;"> Xavier Ysern, PhD </div>		
R/D Init. <div style="text-align: right; margin-top: 10px;"> filename: /nda/20537s10.doc </div>		
DISTRIBUTION: Original: NDA 20-357 cc: HFD-510 Division File/ JWeber / SMoore/ XYsern		

AP

 8/12/98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020357, S010

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

ENVIRONMENTAL ASSESSMENT¹
Metformin Hydrochloride Tablets NDA 20-357
Use of Glucophage® With Insulin

¹This assessment references data previously provided to FDA. Please refer to Amendment 32 (November 8, 1994) to NDA 20-357 - Metformin Hydrochloride Tablets for copies of relevant study reports.

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21 CFR 25.31 (a)

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Section 1. DATE

April 30, 1998

Section 2. NAME OF APPLICANT/PETITIONER:

Bristol-Myers Squibb Company

Section 3. ADDRESS (MAILING)

P.O. Box 4000
Princeton, NJ 08543-4000

Section 4. DESCRIPTION OF PROPOSED ACTION

a. Requested Approval

Bristol-Myers Squibb has filed a Supplemental New Drug Application (SNDA #) pursuant to Section 505 (b) of the Federal Food, Drug and Cosmetic Act for Glucophage® (Metformin Hydrochloride) Tablets, 500 and 850 mg. This Environmental Assessment (EA) is being submitted pursuant to 21 CFR part 25. The original NDA (20-357), submitted to the FDA by Lipha, was approved on March 3, 1995. This NDA was transferred to Bristol-Myers Squibb on January 19, 1995. The original environmental assessment for metformin hydrochloride was filed as Item 3.5 of the Glucophage® NDA and submitted to the FDA as Ammendment #32 on November 8, 1994. A copy of the executive summary for this previous EA is attached as NonConfidential Appendix 1.

b. Need for Action

Metformin hydrochloride is an oral hypoglycemic, currently approved for treatment of non-insulin dependent diabetes mellitus (NIDDM) in conjunction with control of diet, exercise, and/or therapy with sulfonylurea drugs. The SNDA requests the expansion of the labeling to approve the use of this drug together with insulin therapy for the treatment of non-insulin dependent diabetes mellitus.

c. Locations of Use

The tablets are sold to hospitals, clinics and pharmacies throughout the USA for use by both in-patient and out-patient populations.

d. Disposal Sites

At U.S. hospitals, clinics and pharmacies empty, or partially empty, containers will be disposed of according to the facility's procedures. Empty or partially empty containers from homes of patients will typically be disposed of by a community's solid waste management system which could include landfills, incineration and/or recycling. Minimal quantities of unused drug could be disposed of in sewer systems.

Section 5 IDENTIFICATION OF SUBSTANCES THAT ARE THE SUBJECT OF THE PROPOSED ACTION

This NDA is for Glucophage® Tablets. The relevant drug substance and active ingredient is metformin hydrochloride.

a. Nomenclature

i. Established Name (U.S. Adopted Name - USAN)

Metformin hydrochloride

ii. Brand/Proprietary Name/Tradename

Glucophage

iii. Chemical Names

Imidodicarbonimidicdiamide-, N,N-Dimethyl-; hydrochloride (inverted form)

N,N-Dimethylimidodicarbonimidic diamide, hydrochloride (noninverted)

1,1-dimethylbiguanide (synonym)

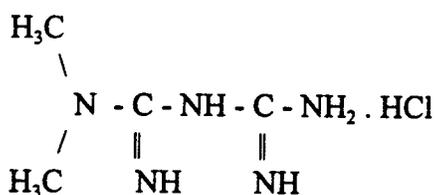
b. Chemical Abstracts Service (CAS) Registration Number

1115-70-4 (hydrochloride); 657-24-9 (free base)

c/d. Molecular Formulas and Molecular Weights

HCl salt:	M.F. C ₄ H ₁₂ ClN ₅	M.W. 165.63
Free Base:	M.F. C ₄ H ₁₁ N ₅	M.W. 129.17

e. **Structural (graphic) Formula**



Section 6 ENVIRONMENTAL ISSUES

a. **Environmental Fate of Released Substances**

i. **Identification of Substances of Interest**

Metformin hydrochloride used for pharmaceutical production must contain less than 0.5% total impurities, and typically contains much less than this amount. It is not metabolized in humans so the substance which enters the environment through patient therapy is metformin hydrochloride itself. This information is documented in the original NDA (20-357) and will not be elaborated further here.

ii. **Physical and Chemical Characterization**

Basic physicochemical properties of metformin hydrochloride are summarized in the data table of the Nonconfidential Appendix. Metformin hydrochloride is very water soluble, has negligible vapor pressure at ambient temperature and is not predicted to adsorb to organic matter. Based on this information, the aquatic compartment is considered to be the environmental compartment of potential concern. This information is documented in the original NDA (20-357) and will not be elaborated further here.

iii. **Environmental Depletion Mechanisms**

Studies to develop this data were conducted according to the FDA Environmental Assessment Technical Assistance Handbook, under GLP regulations, at _____ under the sponsorship of Lipha Pharmaceuticals. Analytical methods were validated as per requirements.

Metformin hydrochloride is not degraded by either hydrolysis or aerobic biodegradation. The compound does not absorb light at wavelengths _____ so a direct photolysis study was not conducted. The primary mechanism for environmental degradation of metformin hydrochloride may involve indirect photolysis, with a calculated half-life of 28.3 days, as estimated in

photolysis studies using acetone as a sensitizer. Therefore, although some depletion of metformin hydrochloride would be expected, "rapid and complete" degradation is not predicted. This information is summarized in the data table of the Nonconfidential Appendix.

iv. Environmental Concentrations

Based on estimated 5-year production volumes, the Maximum Expected Environmental Concentration (MEEC) has been estimated for the aquatic compartment, according to the draft guidance provided by the FDA in February, 1998. This MEEC is equivalent to the Expected Introduction Concentration (EIC). It should be noted that the Expected Environmental Concentration (EEC) is likely to be at least _____ than this due to dilution of water exiting publicly owned treatment works (POTWs). A factor of _____ has been used to account for this dilution. In addition, some degradation as a result of indirect photolytic breakdown may be possible resulting in an even lower EEC. The calculations for the EIC and EEC are shown in the Confidential Appendix 1.

v. Summary

Metformin hydrochloride in the environment might undergo some degradation based on the data from the indirect photolysis study. It is not a volatile substance and is not expected to enter the atmospheric compartments. Based on its K_{oc}, it is not expected to adsorb to organic material in soils. Metformin hydrochloride is very water soluble and if it enters the environment it is likely to remain in the aquatic environment. The maximum expected environmental concentration (after allowing for dilution of output from POTWs) is found in Confidential Appendix 1.

b. Environmental Effects of Released Substances

i. Tiered Approach to Environmental Effects Testing

Although the data of the indirect photolysis study suggest that some degradation of the substance may occur by photolytic mechanisms, the rate of degradation is not sufficient to be considered "rapid and complete". Since the compound has a very low log K_{ow} and is expected to remain in the water compartment, data concerning acute toxicity to aquatic species (*Daphnia magna*) was reviewed

In addition, since acute toxicity for bluegills was also available from the previous NDA submission, this was also reviewed

ii. Microbial Inhibition

The potential for metformin hydrochloride to affect waste water treatment microorganisms was assessed using microbial inhibition studies. The results of these studies indicated that the organisms were quite resistant to metformin hydrochloride with minimum inhibitory concentrations (MIC)

Anabaena, an algae, was most sensitive with a MIC

These data are summarized in the data table of the Nonconfidential Appendix.

iii. Tier 1-2 Acute Toxicity to Aquatic Species

The data table of the Nonconfidential Appendix also contains a summary of the results of the aquatic toxicity studies on *Daphnia magna* and bluegills. The fish were quite resistant to metformin hydrochloride (the no observed effect concentration (NOEC) was _____ than the MEEC). The EC50 (median effective concentration relative to immobilization of *Daphnia*) value for *Daphnia* was also rather high and reflected a _____ margin above the MEEC.

iv. Test Methods and Test Organisms

The microbial inhibition and aquatic toxicity studies described above were performed using test organisms and methods in accordance with the guidance provided in the FDA Environmental Assessment Technical Assistance Handbook, under GLP regulations, at _____ under the sponsorship of Lipha Pharmaceuticals.

c. Summary of Environmental Fate and Effects

Metformin is not likely to undergo rapid and complete degradation in the environment, although some degradation via indirect photolysis is possible. Due to its physicochemical properties, metformin hydrochloride which remains in the environment is likely to partition into the aquatic compartment. In both the microbial inhibition studies and the Ecotoxicological studies, there was a margin of at least _____ between the predicted MEEC (equal to EIC) and the values obtained for MIC, NOEC, and/or EC50 on the Ecotoxicological or microbial inhibition studies. Additionally, there is a margin of at least _____ between the predicted EEC and the MIC, NOEC or EC50 concentrations. Therefore it is anticipated that the projected increase in the volumes of this drug will not pose a significant risk of harm to aquatic organisms or to the microorganisms at POTWs.

Section 7 MITIGATION MEASURES

As significant adverse environmental effects are not predicted, mitigation measures are not warranted.

Section 8 ALTERNATIVES TO THE PROPOSED ACTION

Since significant environmental effects are not predicted to occur, and since mitigation measures are not proposed, consideration of alternatives to the proposed action is not necessary.

Section 9 LIST OF PREPARERS

Eileen Hayes, Sc.D., DABT, Associate Director, Occupational & Environmental Toxicology, has been a practicing toxicologist since 1979 with experience in occupational and environmental toxicology and chemical metabolism. She received the B.S. in Pharmacy from Northeastern University, the Sc.D. in Toxicology from Harvard School of Public Health and post-doctoral training at Brigham & Women's Hospital/ Harvard Medical School.

James E. Kearney, M.Sc., C.I.H., Associate Director, Environmental Health, has been practicing since 1980 with experience in industrial hygiene, safety management and environmental protection. He received a B.A. in Biology from the University of Buffalo and the M.S. in Environmental Health from the University of Cincinnati.

Section 10 REFERENCES

1. Glucophage® (Metformin Hydrochloride) Tablets, 500 and 850 mg, original NDA (20-357), submitted to the FDA by Lipha, was approved on December 29, 1994.
2. Glucophage® (Metformin Hydrochloride) Tablets, 500 and 850 mg, Amendment #32 to NDA 20-357, Environmental Assessment. This was submitted to the FDA on November 8, 1994.
3. Guidance for Industry: Environmental Assessments of Human Drug and Biologics Applications. U.S. Department of Health and Human Services, Food and Drug Administration. Draft Guidance issued on February 12, 1998.

Section 11 APPENDICES

Two nonconfidential and one confidential appendices follow.

NONCONFIDENTIAL APPENDIX 1

**Executive Summary from Amendment #32 (Environmental
Assessment) to NDA 20-357 for Glucophage (Metformin
Hydrochloride) Tablets November 8, 1998**

ITEM 3 — CHEMISTRY, MANUFACTURING AND CONTROLS

EXECUTIVE SUMMARY

This amendment (#32) to our NDA #20-357 for Glucophage® (metformin hydrochloride) reflects a revision as well as additional data to our earlier Environmental Assessment submitted in our NDA application of September 29, 1993 and to its revision (Amendment #27) submitted August 19, 1994. The document format is arranged as required in 21 CFR 25.31(a). The proposed action will provide a new oral antihyperglycemic drug for the treatment of non-insulin-dependent diabetes mellitus (NIDDM) as first-line therapy in selected patients and when hyperglycemia cannot be otherwise managed with available treatments.

The manufacture of metformin HCl will not adversely impact the environment either directly or indirectly. Drug substance will be manufactured in and drug product will be manufactured in both sites operate in compliance with all applicable environmental regulations and are currently approved for manufacturing for worldwide distribution. Thus, no additional environmental impact is anticipated by this action.

Metformin HCl is in the protonated form (monohydrochloride). Metformin itself is a strong base with a pK_a of 12.4. The hydrochloride salt is a freely water-soluble compound (~30% wt/vol) with an undetectable vapor pressure at ambient temperatures due to its high melting point of 225°C. The estimated sorption coefficient (K_{oc}), calculated from the octanol/water partition coefficient, is 4.97.

ITEM 3 – CHEMISTRY, MANUFACTURING AND CONTROLS

Upon use, metformin HCl is excreted unchanged and, based on the calculated K_{oc} of 4.97, it is concluded that it will reside as the hydrochloride salt in the aquatic environmental compartment within the sewage treatment plant and outside in the environment when released as wastewater effluent. Therefore, the effects testing was directed towards the aqueous compartment.

The maximum emitted environmental concentration (MEEC) was calculated to be). The results of environmental fate studies demonstrate that there is no hydrolysis (pH 5, 7, and 9) after 5 days and limited aerobic biodegradation in water (approximately 0.6% $^{14}\text{CO}_2$ production) after 28 days. No absorption was detected in the ultraviolet-visible absorption spectra in the range of 290 to 800 nm at pH 5, 7, and 9; hence, no direct photolysis study was conducted. Nonetheless, an indirect photolysis study was conducted using acetone as a sensitizer. Metformin degraded into three quantifiable components, with the calculated half-life of the parent being 28.3 days. Based on this calculated half-life, the expected environmental concentration (EEC) may be half of the MEEC. In addition, the wastewater effluents from the sewage treatment plants are expected to be released into waterways and because of the continuous, naturally occurring dilution, the EEC will be still lower.

Extensive toxicity testing, from acute to chronic/carcinogenicity studies, demonstrated that toxicity to mammals is very low. Effects studies in representative microorganisms and aquatic species, such as *Daphnia* and fish,

ITEM 3 – CHEMISTRY, MANUFACTURING AND CONTROLS

demonstrated no observable effects at concentrations about 10^5 to 10^6 times the MEEC. The results of these studies are summarized in the following table.

Study Name	Species	Results
Microbial Growth Inhibition (FDA 4.02)	<i>Aspergillus, Penicillium, Chaetomium</i> (fungi), <i>Pseudomonas, Bacillus</i>	No inhibition @ ppm
	<i>Anabaena</i> (alga)	MIC = ppm
	<i>Azotobacter</i> (N_2 -fixing bacterium)	MIC = ppm
<i>Daphnia</i> Acute Toxicity (FDA 4.08)	<i>Daphnia magna</i>	NOEC = mg/L EC ₅₀ (calc.) = mg/L
Freshwater Fish Acute Toxicity (FDA 4.11)	Bluegill (<i>Lepomis macrochirus</i>)	NOEC = mg/L

- NOEC = No-observed-effects concentration
MEEC = Maximum emitted environmental concentration
MIC = Minimum inhibitory concentration
EC₅₀ = Concentration producing 50% immobilization

Based on the results of the physicochemical, fate, and effects testing conducted with metformin HCl, no adverse environmental impact is anticipated.

NONCONFIDENTIAL APPENDIX 2

Data Summary Table

NONCONFIDENTIAL APPENDIX 2

DATA SUMMARY TABLE

Physical/Chemical Characterization	
Water solubility	30.55 %
Partition coefficient (octanol/water) [Log Kow]	0.056 [-1.25]
Vapor Pressure	virtually nil
Sorption Coefficient (Koc), estimated	4.97
Depletion Mechanisms	
Hydrolysis	Does not hydrolyze at 50 degrees C for 5 days at pH values of 5, 7 or 9.
Aerobic Degradation	0.6% conversion to CO ₂ after 28 days.
Photolysis.	Not conducted. No absorbance between 290 and 800 nm.
Indirect Photolysis	T ½ estimated at 28.3 days
Environmental Effects	
Microbial Inhibition: Aspergillus, Penicillium, Chaetomium (fungi), Pseudomonas, Bacillus	No inhibition @ 1000 ppm
Anabaena (algae)	MIC = 100 ppm
Azobacter (Nitrogen fixing bacterium)	MIC = 800 ppm
Daphnia Magna Acute Toxicity (48 hr.)	NOEC = 78 mg/l; EC50 = 130 mg/l
Fish Acute Toxicity (Bluegills) (96 hr.)	NOEC = 982 mg/l

Table abbreviations:

NOEC = No observed effects concentration

MIC = Minimum inhibitory concentration

EC50 = Concentration producing 50% immobilization

CONFIDENTIAL APPENDIX 1

Production Volumes and Expected Environmental Concentrations.

2 PAGES REDACTED

**CONTAINED TRADE
SECRETS and/or
CONFIDENTIAL/
COMMERCIAL
INFORMATION**