DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

TRANSMITTED VIA FACSIMILE

MAR 16 2000

Charles A. Heimbold, Jr.
Chairman and Chief Executive Officer
Bristol-Myers Squibb Company
345 Park Avenue
New York, NY 10154-0037

RE: NDA 20-757 Avapro (irbesartan) tablets
NDA 20-357 Glucophage (metformin hydrochloride) tablets
NDA 20-262 Taxol (paclitaxel)
MACMIS ID #8755

WARNING LETTER

Dear Mr. Heimbold:

This Warning Letter concerns Bristol-Myers Squibb Company's (BMS) dissemination of promotional materials for Avapro (irbesartan), Glucophage (metformin hydrochloride), and Taxol (paclitaxel). As part of its routine monitoring and surveillance program, the Division of Drug Marketing, Advertising, and Communications (DDMAC) has become aware of promotional materials for these products that are false, lacking in fair balance, or otherwise misleading in violation of the Federal Food, Drug, and Cosmetic Act (Act), 21 USC § 331(a), (b), (d), 352(a), (n), 355(a), and applicable regulations.

We have previously issued letters to BMS about these products. The letters objected to BMS' dissemination of promotional materials that were lacking in fair balance, contained misleading safety and efficacy presentations, or contained misleading mechanism of action claims. We have been assured that corrective steps were being taken concerning these issues. In fact, BMS continues to engage in the dissemination of promotional materials for these products that are in violation of the Act for the same or similar reasons. The dissemination of these misleading promotional materials misbrands Avapro, Glucophage, and Taxol.

Avapro (irbesartan) Tablets

Since its October 1997 product launch, BMS has repeatedly promoted Avapro (irbesartan) tablets in violation of the Act and its implementing regulations. Each of the

violations described in the following paragraphs has been communicated to BMS in one or more untitled letters.

Lack of fair balance

Promotional materials are misleading if they fail to present information relating to side effects and contraindications with a prominence and readability that is reasonably comparable with the presentation relating to effectiveness, taking into account all implementing factors and techniques likely to achieve emphasis.

Avapro's approved product labeling (PI) contains a boxed warning concerning the risk of fetal injury or death if Avapro is used during the second or third trimesters of pregnancy. Sales aid B2-A050 contains a two-page spread devoted to presentation of information concerning the safety and tolerability profile of Avapro. On these pages, you present promotional claims, such as "a favorable safety profile," and "Avapro: proven tolerability at all doses." However, information from the boxed warning is not presented with these safety claims. Instead, this important safety information is presented only once, in small type at the bottom of the last page of the eight-page sales aid. Presentation of this risk information in this manner minimizes its importance and is inadequate to convey the serious, and avoidable, risk associated with Avapro therapy. Furthermore, although you mention the existence of the boxed warning on each spread of the sales aid, you do not provide a prominent disclosure of this significant risk anywhere in the eight-page brochure.

Misleading efficacy presentations

Promotional materials are false, lacking in fair balance, or otherwise misleading if they state or suggest that a drug is safer or more effective than a different drug or category of drugs than has been demonstrated by substantial evidence or substantial clinical experience.

In sales aid B2-A050, you graphically present the results of two clinical trials (trial #1 and trial #2)[1,2] that compare specific dosing regimens of Avapro and Cozaar (losartan potassium).[3] The resultant difference in mean trough diastolic blood pressure (DPB)

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1. Kassler-Taub K, Littlejohn T, Elliott W, et al. Comparative efficacy of two angiotensin II receptor antagonists, irbesartan and losartan, in mild-to-moderate hypertension. *American Journal of Hypertension.* 1998, 11(4): 445-453.

2. Oparil S, Guthrie R, Lewin AJ, et al. An elective-titration study of the comparative effectiveness of two angiotensin II-receptor blockers, irbesartan and losartan. *Clinical Therapeutics.* 1998, 20(3): 398-409.

3. Cozaar (losartan potassium) is a product of Merck & Co., Inc.

between the highest once daily dose of Avapro compared to losartan was 3 mmHg for trial #1 and 2.3 mmHg for trial #2. However, in the graphic presentation of these data you prominently state that in trial #1, Avapro provided a 34% greater reduction in DBP than losartan, and in trial #2, Avapro provided a 29% greater reduction in DBP than losartan. This presentation is misleading because it distorts and misrepresents the differences between the drug products, suggesting a much larger difference than was demonstrated in the studies. The presentation of the data (mean differences in DBP of 3 mmHg and 2.3 mmHg) is buried in the significantly less prominent text beneath the bar graph.

Misrepresentation of mechanism of action to imply clinical superiority over other ARBs

In sales aid B2-A050, you present a comparison of the degree and duration of angiotensin II blockade for Avapro, losartan, and valsartan.[4] Your graph of response over time after administration clearly depicts Avapro as providing a greater degree and longer duration of angiotensin II blockade than losartan or valsartan. You also present claims suggesting that these characteristics are clinically relevant, such as "Avapro: sustained ANG II blockade at the AT_1 receptor," and "Degree + duration = sustained ANG II blockade with Avapro." This graphic and textual presentation implies that Avapro is clinically superior to losartan and valsartan because of its degree and duration of angiotensin II blockade. These differences, however, have not been shown to be of clinical significance. Therefore, the suggestion that these differences have clinical meaning or clinical superiority is misleading. This misleading implication is not adequately corrected by the inclusion of a disclaimer that the clinical significance is unknown.

Use of violative "homemade" promotional materials

Your sales representatives have repeatedly disseminated violative "homemade" promotional labeling pieces for Avapro. In previous correspondence, we objected to the dissemination of a "homemade" promotional labeling piece that failed to include any risk information about the use of Avapro, and which did not include the PI. We also objected to the dissemination of a "homemade" promotional labeling piece for Avapro that contained misrepresentations of safety and efficacy and unsubstantiated comparative claims that lacked fair balance, and did not include the PI. BMS acknowledged in its May 3, 1999, letter that its sales representatives had disseminated yet another "homemade" promotional piece for Avapro that contained false or misleading efficacy claims, lacked disclosure of any risk information, and did not include the PI. We have serious concerns about the continuing dissemination of "homemade" promotional materials that fail to disclose critical information about the risk of fetal injury or death if Avapro is taken during the second or third trimesters of pregnancy.

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4. Diovan (valsartan) is a product of Novartis Pharmaceuticals Corporation.

Failure to submit promotional materials pursuant to 21 CFR § 314.81(b)(3)(i)

You also violated the regulations by failing to submit the "homemade" promotional labeling pieces to FDA at the time of initial dissemination as required by 21 CFR § 314.81(b)(3)(i).

In response to our past objections, you stated your intent to revise or discontinue materials for Avapro that contain these violations. With respect to "homemade" materials, you said that your policy prohibits the use of "homemade" materials, and that you had taken action to ensure that these violations would not reoccur. In fact, your October 16, 1998, letter concluded "DDMAC can have confidence that BMS will remain vigilant in enforcing its prohibition against the creation and use of homemade promotional materials by its sales representatives." Despite these reassurances, you have continued to disseminate promotional materials containing the same or similar false or misleading claims.

Glucophage (metformin hydrochloride) Tablets

You disseminated promotional materials for Glucophage that are misleading and in violation of the Act and regulations. Examples include, but are not limited to, the following promotional materials submitted pursuant to the post-marketing reporting requirements: Reprint Carrier (F5-A124), Poster (F5-K239), Direct-to-Consumer (DTC) Advertisement (F5-K132R), Dosing Card (F5-A262), File Card (F5-A261), Sales Aid (F5-A267) and "Timely Information Lunch & Learn" Display (F5-B031). DDMAC finds these materials to be in violation of the Act.

Lack of fair balance

The PI for Glucophage includes a boxed warning concerning lactic acidosis, a rare but serious metabolic complication of metformin treatment. When lactic acidosis occurs, it is fatal in approximately 50% of the cases. The boxed warning includes a discussion of the conditions that increase the risk of developing lactic acidosis, and advises health care providers to inform their patients about the symptoms of lactic acidosis.

In an untitled letter, dated March 9, 1998, we objected to promotional labeling for Glucophage that lacked fair balance, minimized the significance of revisions to the PI that discussed the serious potential risk factors for the development of lactic acidosis, and contained claims that were inconsistent with the PI. In your March 23, 1998, response, you stated "As per DDMAC's recommendation, Bristol-Myers Squibb (BMS) will discontinue use of this and all other promotional materials that contain violative material as discussed in the March 9, 1998 letter from DDMAC."

The reprint carrier (F5-A124), disseminated by BMS at its promotional exhibit booth during the American Society of Health-System Pharmacist (ASHP) Midyear Clinical Meeting, December 5-9, 1999, in Orlando, Florida, fails to include material information about the risk of lactic acidosis that is included in the contraindication, boxed warning, and precautions sections of the Glucophage PI. Specifically, the reprint carrier omits the following serious risk information about the potential for lactic acidosis in certain patient populations:

> "Glucophage is contraindicated in patients with congestive heart failure requiring pharmacologic treatment."
>
> "...treatment of the elderly should be accompanied by careful monitoring of renal function. Glucophage treatment should not be initiated in patients >80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced, as these patients are more susceptible to developing lactic acidosis"

By omitting this important risk information concerning lactic acidosis, the reprint carrier implies that Glucophage may be used safely in a broader patient population than is, in fact, the case.

The promotional pieces for Glucophage referred to on Page 4 lack fair balance and minimize the importance of the information concerning lactic acidosis and other important risks associated with the use of Glucophage. These pieces do not present important risk information, including boxed warning information concerning lactic acidosis, with a prominence and readability reasonably comparable to presentations relating to the effectiveness of the drug. For example, in DTC advertisement F5-K132R risk information is presented in a paragraph at the bottom of the advertisement in small type size. Moreover, this information is presented in a single paragraph across the width of the page, rendering the information extremely difficult to read. In contrast, claims about the effectiveness of Glucophage are presented very prominently using large, bold typeface, and are presented as short, easy to read bullet points for further emphasis. [5]

Moreover, the dosing card F5-A262 and file card F5-A261 disclose information concerning the boxed warning on lactic acidosis, and other important risk information, in a manner similar to the DTC journal advertisement (small type size and paragraphing) under the header "Appropriate patient selection is the key." This header further

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[5] We also note that similar types of presentation have been used on advertisements that have been disseminated in public areas such as subway trains. In those presentations, the risk information in the body of the ad and the "PATIENT INFORMATION ABOUT GLUCOPHAGE" are virtually impossible to read. Thus, the only message communicated to the consumer is unbalanced information about Glucophage.

minimizes the importance of the risk information that follows. These methods of "burying" information, especially risks described in a boxed warning, minimize its importance.

Misleading efficacy presentations

The use of clearly inappropriate data presentations is misleading. For example, the "Timely Information Lunch & Learn" display (F5-B031) is misleading in its presentation of efficacy data relating to the use of Glucophage with insulin derived from a 24 week, double-blind, placebo-controlled study. The study compared Glucophage plus insulin to placebo plus insulin. In such a study, it is only the comparison between the treatment and control groups that is meaningful; the change from baseline in the study drug group is not interpretable without reference to the change from baseline in the control. Indeed it is because the change from baseline is uninformative without reference to a control that the control is needed. Despite this, the reduction from baseline in glycosylated hemoglobin for patients randomized to the Glucophage plus insulin group are presented very prominently, while the corresponding results for patients randomized to the insulin plus placebo arm are presented in a manner that is readable only upon very close examination of the spread. In this case, the change in glycosylated hemoglobin at the final visit in the Glucophage plus insulin group was not significantly different, using analysis of variance, from the change seen in the group that received placebo plus insulin.

Misleading safety presentation

The claim, "Unlike sulfonylureas, Glucophage ***does not produce hypoglycemia*** even in individuals with normal glucose levels (when used alone and under normal circumstances of use)," in the "Timely Information Lunch & Learn" display (F5-B031), is misleading. Hypoglycemia is a risk during normal circumstances of use, which includes use in combination with other hypoglycemic agents. The "Lunch & Learn" display discusses the use of Glucophage in combination therapy with sulfonylureas and with insulin, but fails to disclose that there is a risk of hypoglycemia with the use of Glucophage in combination therapy, even though this risk is clearly identified in the PI. The "PRECAUTIONS" section of the PI states that hypoglycemia could occur during concomitant use with other glucose lowering agents (such as sulfonylureas and insulin). The PI also states that, when initiating combination therapy, the risks of hypoglycemia, its symptoms and treatment, and conditions that predispose patients to its development should be explained to patients.

Misleading mechanism of action presentation

The reprint carrier (F5A-124) is in violation of the Act because it selectively presents information contained in the PI relating to Glucophage's mechanism of action, conveying a misleading impression. Specifically, the reprint carrier includes the

statement "[Metformin] improves insulin sensitivity and thus decreases the insulin resistance that is prevalent in NIDDM" under the header "MECHANISM OF ACTION." This presentation strongly suggests that Glucophage works mainly by reducing insulin resistance. However, the PI describes three distinct mechanisms by which Glucophage acts to reduce glucose levels ["Glucophage decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity (increases peripheral glucose uptake and utilization)"]. You have not demonstrated that improving insulin sensitivity, one of three mechanisms listed in the PI, is Glucophage's main mechanism of action.

Similarly, the "Lunch & Learn" display (F5-B031) selectively presents information contained in the PI relating to Glucophage's mechanism of action. Specifically, the stages associated with increasing levels of insulin resistance are presented in conjunction with claims such as "GLUCOPHAGE first-line makes the body's own insulin work better," and "...GLUCOPHAGE makes exogenous insulin work better." Moreover, the claim "Glucophage improves glycemic control by improving hepatic and peripheral insulin sensitivity, which results in a decrease in hepatic glucose production and an increase in peripheral glucose uptake" is offered as the answer to the question "Glucophage improves insulin sensitivity at which sites?" These representations also strongly suggest that Glucophage works mainly by reducing insulin resistance.

In previous correspondence about these types of violations, we objected to an audiotape and script that included claims such as "[Glucophage's] major mechanism of action is to improve...insulin sensitivity" and "With Glucophage, we can *target* insulin resistance...." We also objected to a promotional letter that included the claim "Glucophage lowers blood glucose levels by decreasing insulin resistance...." Although you previously agreed to discontinue promotional materials containing these claims, the same or similar misleading messages continue to appear.

Taxol (paclitaxel)

You disseminated journal advertisements (K4-K033R, K4-K032) for Taxol that lack fair balance and broaden the indication for Taxol, in violation of the Act.

Lack of fair balance

You present the most common adverse events at the bottom of these advertisements in small type size. This presentation is lacking in fair balance because it is not presented with a prominence and readability reasonably comparable to the presentation of information pertaining to efficacy. In addition, the journal advertisements fail to include material information about the risks associated with Taxol therapy. Specifically, the journal advertisements omit serious risk information that appears as a boxed warning in the PI. For example, the following risks from the boxed warning section of the PI are not disclosed in the advertisements:

- Anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred in 2%-4% of patients receiving Taxol in clinical trials. Fatal reactions have occurred in patients despite premedication. All patients should be pretreated with corticosteroids, diphenhydramine, and H2 antagonists.

- Taxol therapy should not be given to patients with solid tumors who have baseline neutrophil counts of less than 1500 cells/mm3 and should not be given to patients with AIDS related Kaposi's sarcoma if the baseline neutrophil count is less than 1000 cells/mm3. In order to monitor the occurrence of bone marrow suppression, primarily neutropenia, which may be severe and result in infection, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving Taxol.

By omitting this important risk information, these advertisements imply that Taxol is safer, has fewer, or less incidence of, or less serious, side effects than is, in fact, the case.

Finally, the claim "In general, Taxol is well tolerated" appears in these advertisements. The incidence rates for some of the most common adverse events listed in the PI are alopecia (87%), peripheral neuropathy (79%), anemia (78%), neutropenia (52%), arthralgia/myalgia (60%), nausea/vomiting (52%), and diarrhea (38%). Given the frequency and potential severity of adverse reactions associated with Taxol therapy, your rather extraordinary representation that Taxol is "well tolerated" is misleading. This representation overstates the safety of Taxol and minimizes the importance of the serious risks associated with Taxol therapy, risks well described in the PI, which includes a boxed warning.

Broadening of Indication

The advertisements claim that Taxol is "Clearly Versatile," and has "Proven Activity." However, you have not disclosed the conditions or patient populations for which Taxol is indicated. By omitting the specific indications to provide context to these broad claims, your advertisement suggests that the drug is more useful in a broader range of conditions or patients than has been demonstrated by substantial evidence.

Conclusions and Requested Actions

We are seriously concerned that the dissemination of the aforementioned promotional materials for Avapro, Glucophage, and Taxol demonstrates a continuing pattern and practice by BMS of failing to disclose or of minimizing risk information, and presenting misleading safety and efficacy claims and representations. BMS' previous assurances have not resulted in promotional materials that are in compliance with the Act and regulations. We therefore ask that you provide a detailed response to the issues raised

in this Warning Letter on or before March 31, 2000. This response should contain an action plan that includes:

1. Immediately ceasing the dissemination of all promotional activities and materials for these products that contain the same or similar violations described in this letter.

2. Reviewing its promotional materials for all of its products and discontinuing or revising any materials with the same or similar violations.

3. Submitting a written statement of your intent to comply with "1" and "2" above.

4. Submitting a comprehensive and multi-faceted action plan to disseminate corrective messages about the issues discussed in this letter to the audiences who received your misleading messages.

If you have any questions or comments, please contact Mark Askine, R.Ph., or Janet Norden, MSN, RN by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-42, Rm. 17B-20, 5600 Fishers Lane, Rockville, MD 20857. DDMAC reminds you that only written communications are considered official.

In all future correspondence regarding this particular matter, please refer to MACMIS ID #8755 in addition to the NDA numbers.

Failure to respond to this letter may result in regulatory action, including seizure or injunction, without further notice.

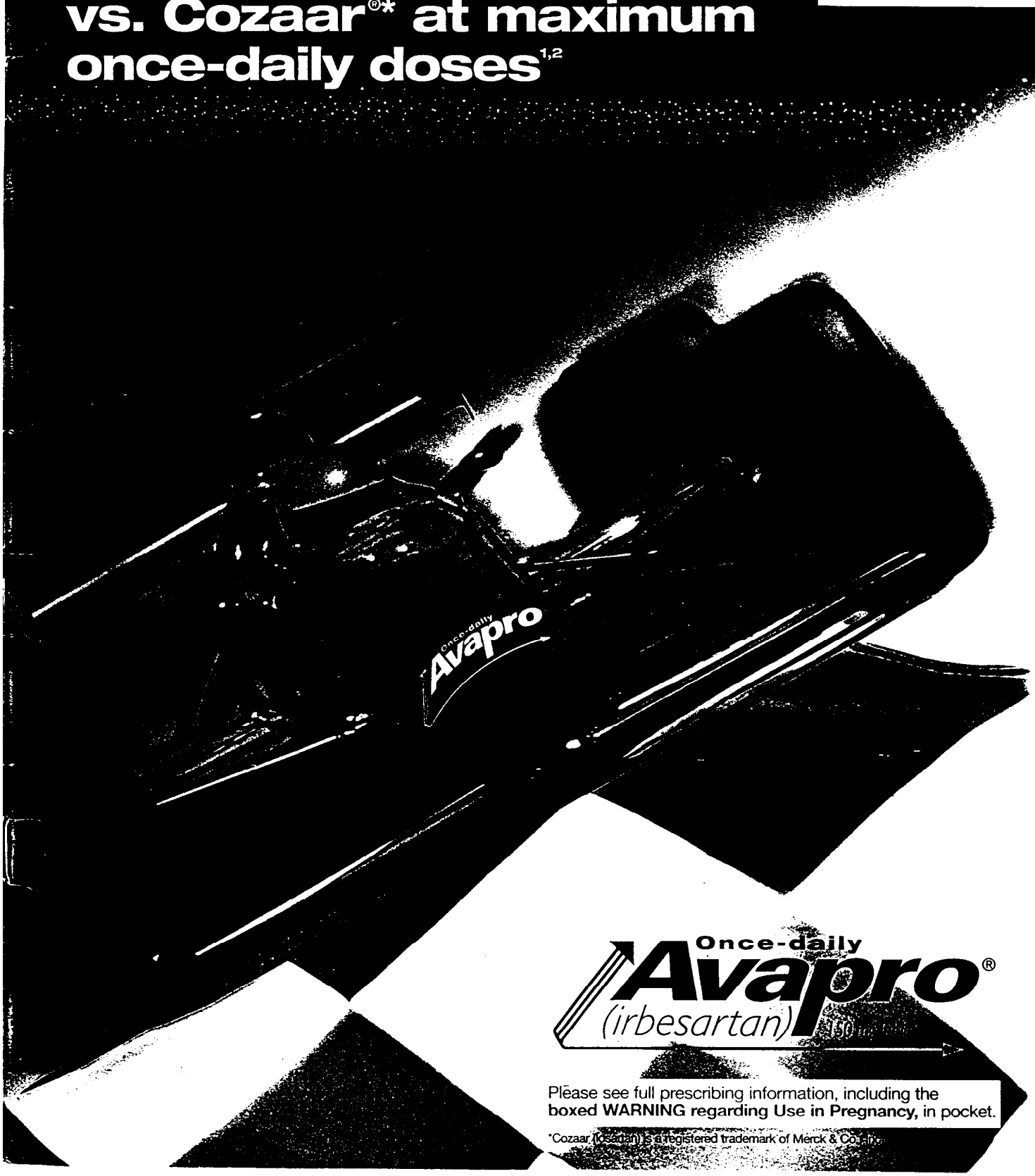
Sincerely,

/S/

Thomas W. Abrams, R.Ph, MBA
Director
Division of Drug Marketing,
Advertising and Communications

B2-A050

Only one ARB has proven superior efficacy vs. Cozaar®* at maximum once-daily doses[1,2]



Once-daily
Avapro®
(irbesartan)

Please see full prescribing information, including the **boxed WARNING regarding Use in Pregnancy,** in pocket.

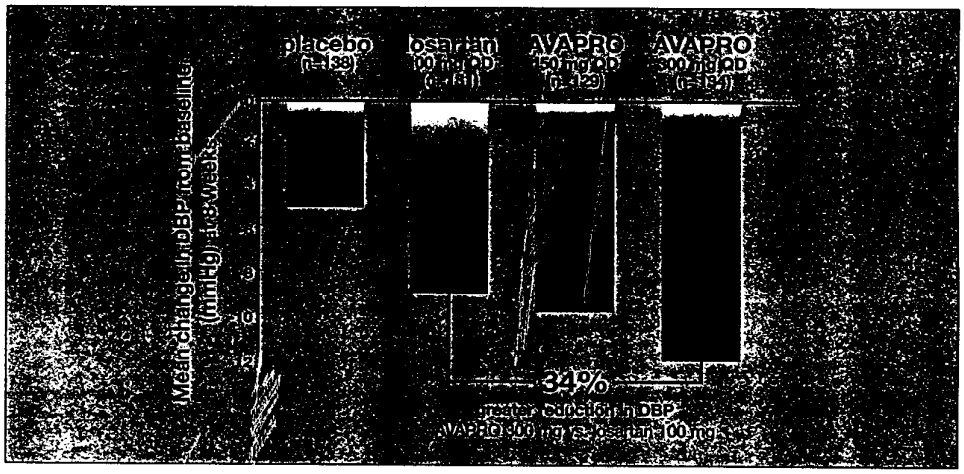
*Cozaar (losartan) is a registered trademark of Merck & Co., Inc.

AVAPRO—the only ARB
Cozaar® at maximum

Significantly more effective in reducing blood pressure at the maximum QD doses

PROVEN ONCE

Study 1 description: *an 8-week, randomized, double-blind, placebo-controlled, comparison study including men and women with DBP 95–110 mmHg; mean baseline blood pressure 154/101; mean age 54 years. Patients evaluated at 8 weeks were receiving once-daily doses of either AVAPRO 150 mg (n=129), AVAPRO 300 mg (n=134), losartan 100 mg (n=131), or placebo (n=138).*



Comparison of usual starting and **maximum** once-daily doses of AVAPRO to the usual **maximum** once-daily dose of losartan

Primary endpoint: *mean change from baseline in DBP (mmHg) at week 8. AVAPRO 300 mg QD (–11.7 mmHg) was statistically significantly superior vs. losartan 100 mg QD (–8.7 mmHg)* (P<0.01), *a 3-mmHg difference. All drugs showed significantly greater decreases in DBP vs. placebo (–4.9 mmHg)* (P<0.01).

Mean change with AVAPRO 150 mg QD starting dose (–9.7 mmHg) was numerically greater but not statistically significant vs. losartan 100 mg QD maximum dose (–8.7 mmHg).

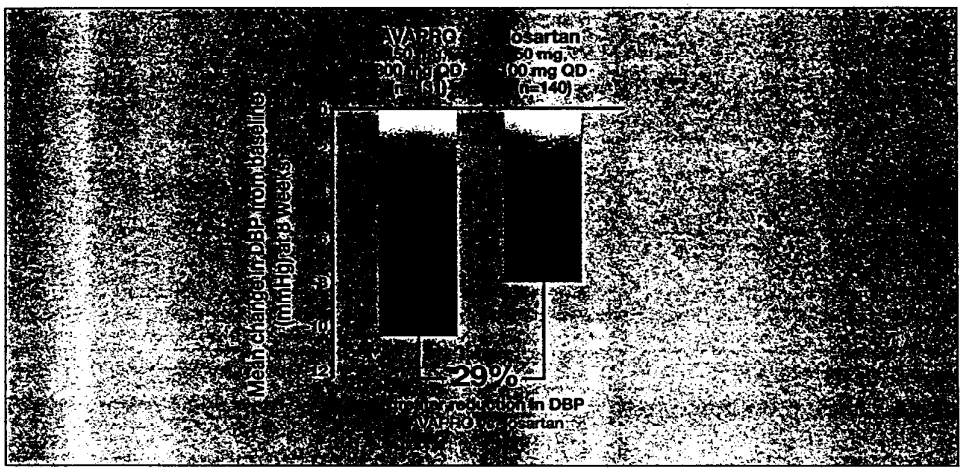
AVAPRO is contraindicated in patients who are hypersensitive to any component of this product.

proven superior to once-daily doses[1,2]

...proven in two head-to-head clinical studies[1,2]*

PROVEN TWICE

Study 2 description: *a 12-week, randomized, double-blind, elective-titration, comparison study. Mild-to-moderate hypertensive patients initially received either AVAPRO 150 mg once daily or losartan 50 mg once daily. Patients not adequately controlled after 4 weeks of therapy were titrated to AVAPRO 300 mg or losartan 100 mg QD. Patient distribution at 8 weeks: AVAPRO (n=131) 150 mg 47%, 300 mg 53%; losartan (n=140) 50 mg 39%, 100 mg 61%.*



Comparison of usual starting and **maximum** once-daily doses of AVAPRO and losartan

Primary endpoint: *mean change from baseline in DBP (mmHg) at week 8. AVAPRO 150 mg or 300 mg QD (–10.2 mmHg) was statistically significantly superior vs. losartan 50 mg or 100 mg QD (–7.9 mmHg) (P<0.02), a 2.3-mmHg difference.*

****A comparison between QD AVAPRO and BID losartan was not made in these studies.***

Once-daily **Avapro®** (irbesartan) 150 mg Tablets

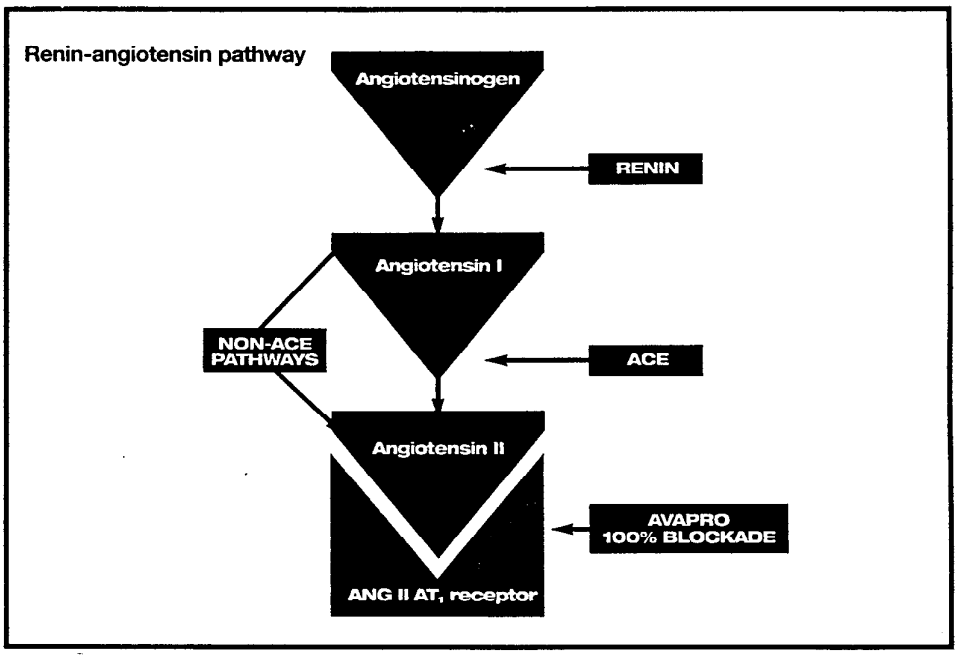
Please see full prescribing information, including the **boxed WARNING regarding Use in Pregnancy,** in pocket.

AVAPRO efficacy | AT_1 receptor blockade | Tolerability & safety

ARBs block ANG II at the AT_1 receptor

Unlike ACEIs, ARBs block angiotensin II (ANG II) regardless of metabolic pathway

The clinical significance of ANG II receptor blockade is unknown.



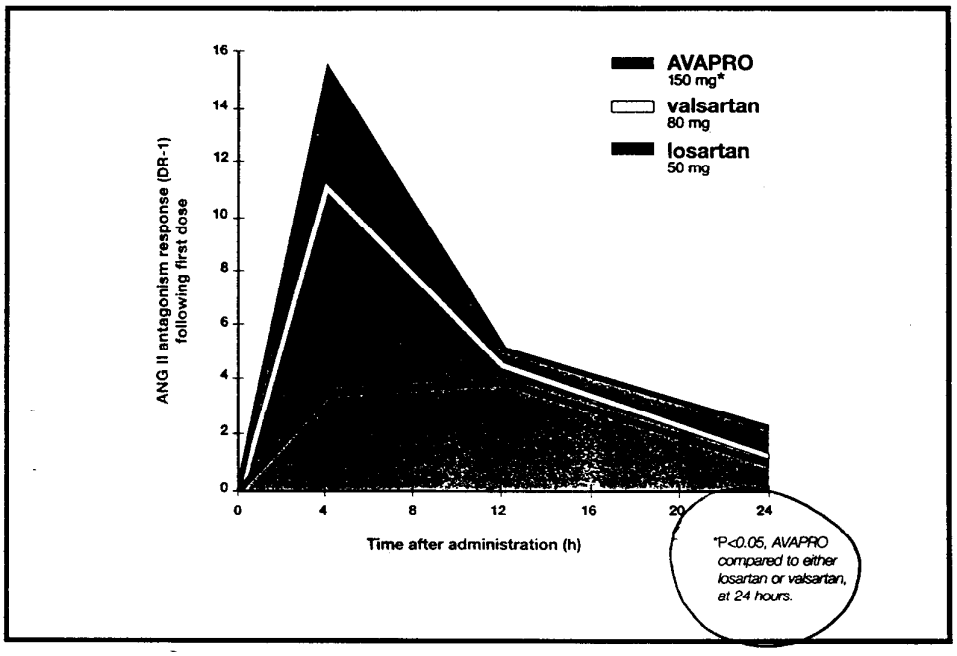
- ACEIs only inhibit ANG II formation via ACE pathway
- ARBs block ANG II at the AT_1 receptor—**the final common pathway for all known pressor ANG II effects**
  —eg, increased vasoconstriction, increased sodium reabsorption and blood volume
- AVAPRO is not associated with an increased incidence of dry cough, as is typically associated with ACE inhibitors[3]
- No difference between AVAPRO and placebo (2.8% vs. 2.7%) in the incidence of cough in AVAPRO clinical trials (n=2,606)[3]

AVAPRO—100% blockade at the AT_1 receptor

AVAPRO: sustained ANG II blockade at the AT_1 receptor

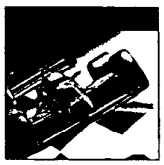
Degree and duration of ANG II blockade: comparison of AVAPRO, losartan and valsartan[3]

The clinical significance of ANG II receptor blockade is unknown.



Double-blind, randomized, 3-period, crossover study in 18 normotensive male subjects taking AVAPRO 150 mg, losartan 50 mg or valsartan 80 mg. Degree and duration of ANG II blockade was measured 24 hours after a single starting dose.

Degree + Duration = Sustained ANG II blockade with AVAPRO®



Once-daily **Avapro®** (irbesartan) 150 mg Tablets

Please see full prescribing information, including the **boxed WARNING regarding Use in Pregnancy,** in pocket.

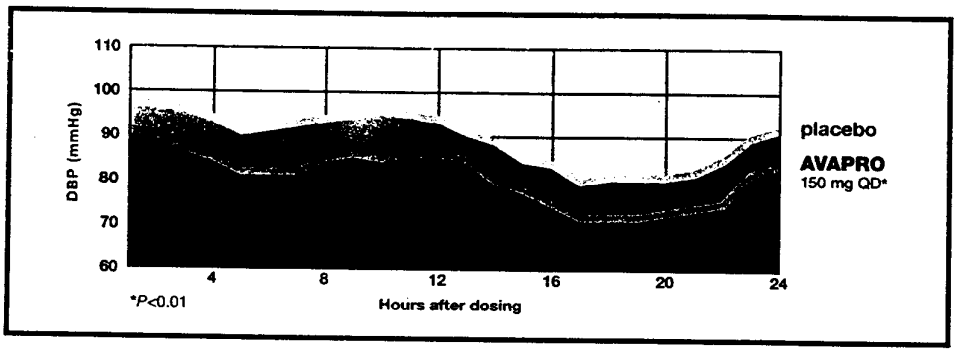
AT_1 receptor blockade

Tolerability & safety

AVAPRO: true QD dosing

Starting dose of 150 mg QD provides 24-hour blood pressure response[4]

Reduction of ambulatory blood pressure



Ambulatory diastolic blood pressure at week 8 of treatment in patients with mild-to-moderate hypertension treated with AVAPRO 150 mg QD (n=47) or placebo QD (n=44). Patients were instructed to take their study drug once a day between 7 am and 10 am throughout the study. Ambulatory blood pressure monitoring was initiated with drug administration.

- Starting-dose efficacy regardless of age, race or gender†

A favorable safety profile

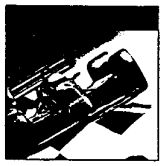
- No dosage adjustment needed in the elderly or in patients with renal or hepatic impairment
  - *—initiation of antihypertensive therapy may cause symptomatic hypotension in patients with intravascular volume depletion or sodium depletion, eg, in patients treated vigorously with diuretics or in patients on dialysis. Such volume depletion or sodium depletion should be corrected prior to administration of AVAPRO (irbesartan), or a low starting dose should be used*
- No clinical effect on key metabolic parameters: lipids, glucose, serum potassium or uric acid
- No drug-drug interactions reported
  - *—drug interaction studies were conducted with hydrochlorothiazide, digoxin, warfarin and nifedipine*

†*Safety and effectiveness in pediatric patients have not been established. The blood pressure effect was somewhat less in blacks (usually a low-renin population).*

AVAPRO: proven tolerability at all doses

- Fewer patients discontinued AVAPRO than placebo (3.3% vs. 4.5%)
  - *—AVAPRO tolerability similar to placebo at all doses, eg, cough (2.8% vs. 2.7%) and orthostatic hypotension (0.4% vs. 0.2%)*
- In placebo-controlled clinical trials, there were no significant differences in adverse events between AVAPRO and placebo that occurred in at least 1% of patients treated with AVAPRO and at a higher incidence versus placebo

	AVAPRO (n=1,965)	placebo (n=641)
Diarrhea	3%	2%
Dyspepsia/heartburn	2%	1%
Musculoskeletal trauma	2%	1%
Fatigue	4%	3%
Upper respiratory infection	9%	6%



Once-daily Avapro® (irbesartan) 150 mg Tablets

Please see full prescribing information, including the **boxed WARNING regarding Use in Pregnancy,** in pocket.

Only AVAPRO has proven superior blood pressure reduction vs. Cozaar® at maximum once-daily doses[1,2]

- Starting dose efficacy regardless of age, race or gender*
- Excellent tolerability profile
- AVAPRO provides 100% blockade at the AT_1 receptor
  The clinical significance of ANG II receptor blockade is unknown.
- AVAPRO offers true QD dosing at the 150 mg starting dose†

**The safety and effectiveness of AVAPRO in pediatric patients have not been established. The blood pressure effect was somewhat less in blacks (usually a low-renin population.)*

†Volume- or sodium-depleted patients (eg, patients vigorously treated with diuretics or on hemodialysis) should be corrected prior to administration of AVAPRO, or a lower initial dose of AVAPRO (75 mg) should be used to avoid possible symptomatic hypotension.

In placebo-controlled clinical trials, there were no significant differences in adverse events between AVAPRO and placebo that occurred in at least 1% of patients treated with AVAPRO and at a higher incidence versus placebo. These included diarrhea (3% vs. 2%), dyspepsia/heartburn (2% vs. 1%), musculoskeletal trauma (2% vs. 1%), fatigue (4% vs. 3%) and upper respiratory infection (9% vs. 6%).

Efficacy and tolerability for first-line therapy

Once-daily **Avapro®** (irbesartan) 150 mg Tablets

NOW, when your patients need more than AVAPRO or HCTZ alone...

150/12.5 mg 300/12.5 mg

NEW Once-daily **Avalide®** (irbesartan/hydrochlorothiazide) 150/12.5 mg Tablets

AVALIDE is not indicated for first-line therapy.

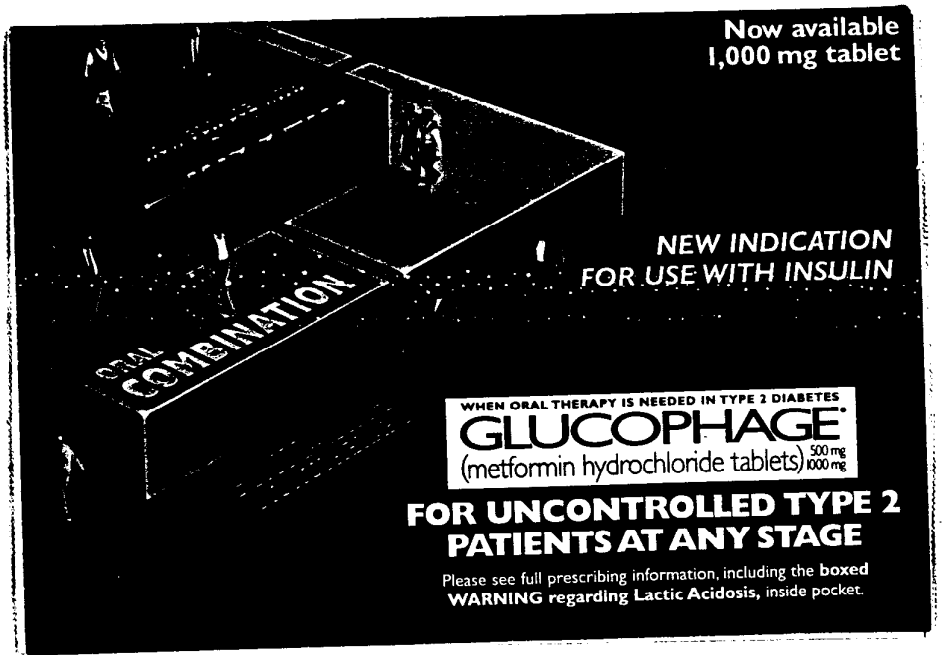
—a patient whose blood pressure is inadequately controlled by irbesartan or HCTZ alone may be switched to QD AVALIDE

USE IN PREGNANCY: When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, AVAPRO or AVALIDE should be discontinued as soon as possible. **See WARNINGS: Fetal/Neonatal Morbidity and Mortality.**

Please see full prescribing information and references in pocket.

Bristol-Myers Squibb Company sanofi 59-991361

 B2-A050 May 1999 Printed in USA



FRONT

F5-A261

WHEN ORAL THERAPY IS NEEDED IN TYPE 2 DIABETES

GLUCOPHAGE®

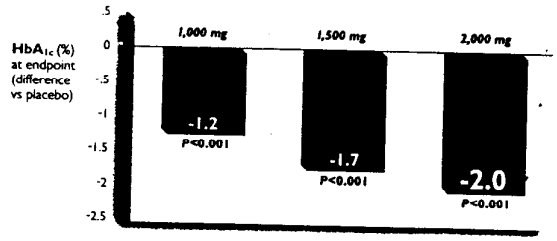
(metformin hydrochloride tablets) 500 mg 1000 mg

Now available 1,000 mg tablet

TITRATE GLUCOPHAGE TO HELP ACHIEVE NORMAL GLUCOSE LEVELS

BID dosing: First-line and in combination with a sulfonylurea

- Start with 1,000 mg/day—titrate to lowest effective dose to achieve normal or near-normal glucose levels.
- GLUCOPHAGE reduces HbA_{1c} by 2% (difference vs placebo) at 2,000 mg/day, as demonstrated in a dose-response trial.[1]



Results of a double-blind, placebo-controlled, dose-response trial at endpoint. Based on intent-to-treat data. 11 weeks of treatment began after a 3-week washout period. 451 randomized, type 2 patients: GLUCOPHAGE 500 mg, n=73; 1000 mg, n=73; 1500 mg, n=76; 2000 mg, n=73; 2500 mg, n=77; placebo, n=79. At 500 mg/day, the reduction in HbA_{1c} was 0.9% ($P<0.01$). At 2500 mg/day, the reduction in HbA_{1c} was 1.6% ($P<0.001$). In the placebo group, HbA_{1c} increased by 1.2%. Values for GLUCOPHAGE represent mean difference between placebo and GLUCOPHAGE.[1]

- **850 and 1,000 mg tablets also available to assist in titration.**
- Some patients may benefit from 2,550 mg/day, the ***maximum dosage*** of GLUCOPHAGE.

NEW

Dosing in combination with insulin

- Maintain current insulin dose.
- Start with 500 mg/day and increase dosage by one 500 mg tablet each week, up to 2500 mg/day, or until adequate glycemic control is achieved.
- **Decrease insulin dose by 10%–25% when FPG decreases to <120 mg/dL.**

Reference: 1. Garber AJ, Duncan TG, Goodman AM, et al: Efficacy of metformin in type II diabetes: results of a double-blind, placebo-controlled, dose-response trial. *Am J Med* 103(6):491-497, 1997.

Please see full prescribing information, including the **boxed WARNING regarding Lactic Acidosis,** inside pocket.

WHEN ORAL THERAPY IS NEEDED IN TYPE 2 DIABETES

GLUCOPHAGE® (metformin hydrochloride tablets) 500 mg 1000 mg

FOR UNCONTROLLED TYPE 2 PATIENTS AT ANY STAGE

Choose GLUCOPHAGE as monotherapy

Add GLUCOPHAGE to patients inadequately controlled on sulfonylurea therapy

NEW Add GLUCOPHAGE to insulin therapy to improve glycemic control

Choose GLUCOPHAGE for weight and lipid benefits

Appropriate patient selection is key

❖ GLUCOPHAGE is contraindicated in patients with renal disease or dysfunction (serum creatinine levels ≥1.5 mg/dL in males, ≥1.4 mg/dL in females); chronic metabolic acidosis, including diabetic ketoacidosis; CHF requiring pharmacologic treatment. GLUCOPHAGE should not be initiated in patients ≥80 years of age unless creatinine clearance has been assessed and found to be normal. GLUCOPHAGE should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis. *Temporarily* discontinue in patients receiving *intravascular* iodinated contrast materials for radiologic studies. Avoid in patients with impaired hepatic function or excessive alcohol intake (acute or chronic). Lactic acidosis, a rare and potentially life-threatening condition (if cases occur, up to half may be fatal), has been reported worldwide in approximately 0.03 cases per 1,000 patient-years, and occurs primarily in type 2 diabetic patients with significant renal insufficiency. To minimize the risk of lactic acidosis, which can be caused by the accumulation of GLUCOPHAGE, appropriate patient selection and adherence to prescribing guidelines are important. Patient Package Insert lists symptoms and predisposing conditions to be discussed with patients. Diarrhea, nausea, vomiting, abdominal bloating, anorexia, or flatulence may occur (30% more often than with placebo), especially during initiation of therapy. Not recommended for pediatric patients or pregnant women. The UGDP study suggested increased cardiovascular risk with some oral antidiabetic agents.

see full prescribing information, including the **boxed WARNING regarding Lactic Acidosis,** inside pocket.

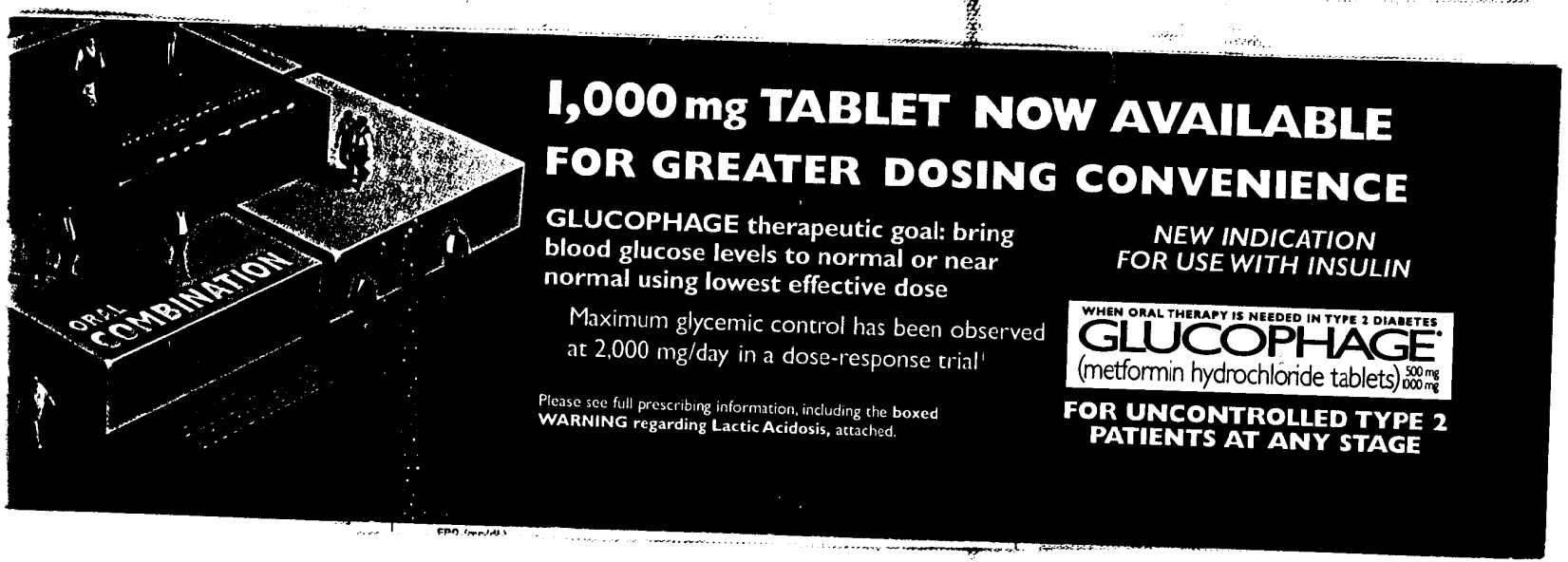
OPHAGE is a registered trademark of LIPHA s.a. Licensed to Bristol-Myers Squibb Company.

Watch 1-800-332-1088 is available to report serious adverse events for any drug.

Bristol-Myers Squibb Company

 F5-A261 Issued: January 1999 Printed in USA ♻ Printed on recyclable paper

Back



Front

E5-A262

Appropriate patient selection is key

❖ GLUCOPHAGE is contraindicated in patients with renal disease or dysfunction (serum creatinine levels ≥1.5 mg/dL in males, ≥1.4 mg/dL in females); chronic metabolic acidosis, including diabetic ketoacidosis; CHF requiring pharmacologic treatment. GLUCOPHAGE should not be initiated in patients ≥80 years of age unless creatinine clearance has been assessed and found to be normal. GLUCOPHAGE should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis. *Temporarily* discontinue in patients receiving *intravascular* iodinated contrast materials for radiologic studies. Avoid in patients with impaired hepatic function or excessive alcohol intake (acute or chronic). Lactic acidosis, a rare and potentially life-threatening condition (if cases occur, up to half may be fatal), has been reported worldwide in approximately 0.03 cases per 1,000 patient-years, and occurs primarily in type 2 diabetic patients with significant renal insufficiency. To minimize the risk of lactic acidosis, which can be caused by the accumulation of GLUCOPHAGE, appropriate patient selection and adherence to prescribing guidelines are important. Patient Package Insert lists symptoms and predisposing conditions to be discussed with patients. Diarrhea, nausea, vomiting, abdominal bloating, anorexia, or flatulence may occur (30% more often than with placebo), especially during initiation of therapy. Not recommended for pediatric patients or pregnant women. The UGDP study suggested increased cardiovascular risk with some oral antidiabetic agents.

Reference: 1. Garber AJ, Duncan TG, Goodman AM, et al: Efficacy of metformin in type II diabetes: results of a double-blind, placebo-controlled, dose-response trial. *Am J Med* 103(6):491-497, 1997.

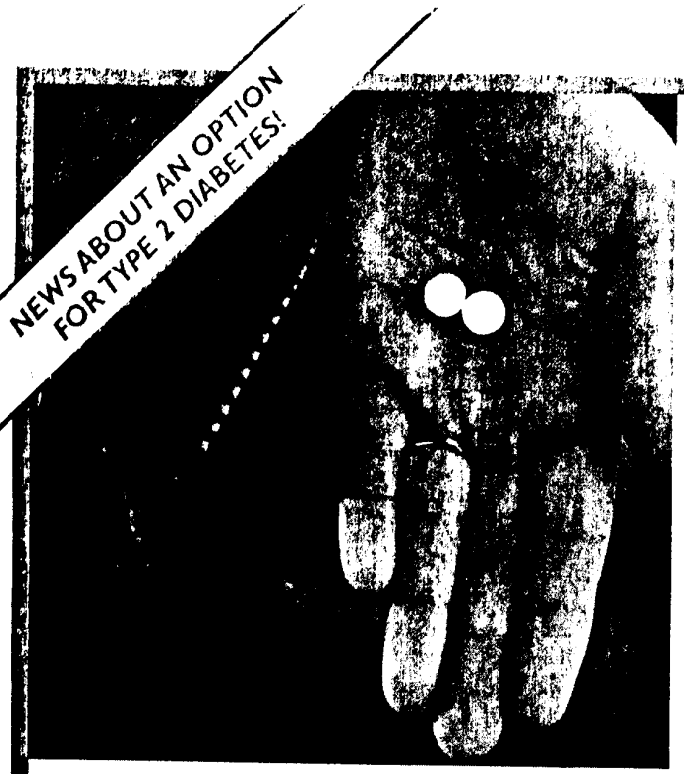
Please see full prescribing information, including the **boxed WARNING regarding Lactic Acidosis,** attached.

Bristol-Myers Squibb Company

F5-A262 Issued: January 1999 Printed in USA ♻ Printed on recyclable paper

Back

FS-K132R



If your DIABETES is uncontrolled... GLUCOPHAGE can help.

GLUCOPHAGE (pronounced "glue-ko-fahj") is the most prescribed type 2 diabetes pill.

- **GLUCOPHAGE,** along with diet and exercise, can be used alone, with pills called sulfonylureas, and now, with insulin.
- **GLUCOPHAGE®** (metformin hydrochloride tablets) lowers blood sugar and may reduce the amount of insulin you need.
- With **GLUCOPHAGE,** your weight should stay the same or you may even lose some.

Controlling your blood sugar is important because it can prevent or delay complications such as blindness and amputations.

ASK YOUR DOCTOR ABOUT...

GLUCOPHAGE®
(Metformin Hydrochloride Tablets)500 mg

For more information, call 1-800-427-5141. **THE MOST PRESCRIBED DIABETES PILL**

There is additional important information about Glucophage you should know. The most serious side effect associated with Glucophage is called lactic acidosis, which is rare and has occurred in one in 33,000 patients on Glucophage over the course of one year. If lactic acidosis occurs, it can be fatal in up to half the cases. You should not take Glucophage if you have kidney disease or dysfunction, if you are 80 or older (unless you have first had your kidneys tested), if you are taking medication for congestive heart failure, if you have a history of liver disease, or if you drink alcohol excessively. The most common side effects are minor ones such as diarrhea, nausea, and upset stomach, which usually occur during the first few weeks on Glucophage. Please see additional important patient information below.

Bristol-Myers Squibb Company

www.glucophage.com

PATIENT INFORMATION ABOUT GLUCOPHAGE®

(metformin hydrochloride tablets)

Rx only

500 mg, 850 mg, and 1000 mg

WARNING: A small number of people who have taken Glucophage have developed a serious condition called lactic acidosis. Properly functioning kidneys are needed to help prevent lactic acidosis. Most people with kidney problems should not take Glucophage. (See Question Nos. 10-14)

Q1. Why do I need to take GLUCOPHAGE?
Your doctor has prescribed GLUCOPHAGE (GLUE-coe fahj) to treat your type 2 diabetes. This is also known as non-insulin dependent diabetes mellitus.

Q2. What is type 2 diabetes?
People with diabetes are not able to make enough insulin and/or respond normally to the insulin their body does make. When this happens, sugar (glucose) builds up in the blood. This can lead to serious medical problems including kidney damage, amputations and blindness. Diabetes is also closely linked to heart disease. The main goal of treating diabetes is to lower your blood sugar to a normal level.

Q3. Why is it important to control type 2 diabetes?
Studies have shown that good control of blood sugar can prevent or delay complications such as blindness.

Q4. How is type 2 diabetes usually controlled?
High blood sugar can be lowered by diet and exercise, by a number of oral medications and by insulin injections. Before taking GLUCOPHAGE, you should first try to control your diabetes by exercise and weight loss. Even if you are taking GLUCOPHAGE, you should still exercise and follow the diet recommended for your diabetes.

Q5. Does GLUCOPHAGE work differently from other glucose-control medications?
Yes. It does. Until GLUCOPHAGE (metformin hydrochloride tablets) was introduced, all the available oral glucose control medications were from the same chemical group called sulfonylureas. These drugs lower blood sugar primarily by causing more of the body's own insulin to be released. GLUCOPHAGE (metformin hydrochloride tablets) lowers the amount of sugar in your blood by helping your body respond better to its own insulin. GLUCOPHAGE does not cause your body to produce more insulin. Therefore, GLUCOPHAGE rarely causes hypoglycemia (low blood sugar) and it doesn't usually cause weight gain.

Q6. What happens if my blood sugar is still too high?
When blood sugar cannot be lowered enough by either GLUCOPHAGE or a sulfonylurea, the two medications may be effective taken together. However, if you are unable to maintain your blood sugar with diet, exercise and glucose control medication taken orally, then your doctor may prescribe injectable insulin to control your diabetes.

Q7. Why would I take GLUCOPHAGE if I am already on insulin?
Because adding GLUCOPHAGE to insulin can help you better control your blood sugar while reducing the insulin dose and possibly reducing your weight.

Q8. Can GLUCOPHAGE cause side effects?
GLUCOPHAGE, like all blood sugar lowering medications, can cause side effects in some patients. Most of these side effects are minor and will go away after you've taken GLUCOPHAGE for a while. However, there are also serious, but rare side effects related to GLUCOPHAGE (see below).

Q9. What kind of side effects can GLUCOPHAGE cause?
If side effects occur, they usually occur during the first few weeks of therapy. They are normally minor ones such as diarrhea, nausea and upset stomach. Taking your GLUCOPHAGE with meals can help reduce these side effects.

Although these side effects are likely to go away, call your doctor if you have severe discomfort or if these effects last for more than a few weeks. Some patients may need to have their dose lowered or stop taking GLUCOPHAGE, either temporarily or permanently. Although these problems occur in up to one third of patients when they first start taking GLUCOPHAGE, you should tell your doctor if the problems come back or start later on during the therapy.

About three out of one hundred people report having a temporary unpleasant or metallic taste when they start taking GLUCOPHAGE.

Q10. Are there any serious side effects that GLUCOPHAGE can cause?
GLUCOPHAGE rarely causes serious side effects. The most serious side effect that GLUCOPHAGE can cause is called lactic acidosis.

Q11. What is lactic acidosis and can it happen to me?
Lactic acidosis is caused by a buildup of lactic acid in the blood. Lactic acidosis associated with GLUCOPHAGE is rare and has occurred mostly in people whose kidneys were not working normally. Lactic acidosis has been reported in about one in 33,000 patients taking GLUCOPHAGE (metformin hydrochloride tablets) over the course of a year. Although rare, if lactic acidosis does occur, it can be fatal in up to half the cases.

It's also important for your liver to be working normally when you take GLUCOPHAGE. Your liver helps remove lactic acid from your bloodstream.

Your doctor will monitor your diabetes and may perform blood tests on you from time to time to make sure your kidneys and your liver are functioning normally.

There is no evidence that GLUCOPHAGE causes harm to the kidneys or liver.

Q12. Are there other risk factors for lactic acidosis?
Your risk of developing lactic acidosis from taking GLUCOPHAGE is very low as long as your kidneys and liver are healthy. However, some factors can increase your risk because they can affect kidney and liver function. You should discuss your risk with your physician. You should not take GLUCOPHAGE if:

- You have chronic kidney or liver problems.
- You have congestive heart failure which is treated with medications (e.g., digoxin (Lanoxin®) or furosemide (Lasix®))
- You drink alcohol excessively (all the time or short term "binge" drinking).
- You are seriously dehydrated (have lost a large amount of body fluids).
- You are going to have certain x-ray procedures with injectable contrast agents.
- You are going to have surgery.
- You develop a serious condition such as a heart attack, severe infection or a stroke.
- You are 80 years of age and have NOT had your kidney function tested.

Q13. What are the symptoms of lactic acidosis?
Some of the symptoms include: feeling very weak, tired or uncomfortable, unusual muscle pain, trouble breathing, unusual or unexpected stomach discomfort, feeling cold, feeling dizzy or lightheaded, or suddenly developing a slow or irregular heartbeat.

If you have these symptoms, or if your medical condition has suddenly changed, stop taking GLUCOPHAGE and call your doctor right away. Lactic acidosis is a medical emergency that must be treated in a hospital.

Q14. What does my doctor need to know to decrease my risk of lactic acidosis?
Tell your doctor if you have an illness that results in severe vomiting, diarrhea and/or fever, or if your intake of fluids is significantly reduced. These situations can lead to severe dehydration and it may be necessary to stop taking GLUCOPHAGE temporarily.

You should let your doctor know if you are going to have any surgery or specialized x-ray procedures that require injection of contrast agents. GLUCOPHAGE therapy will need to be stopped temporarily in such instances.

Q15. Can I take GLUCOPHAGE with other medications?
Remind your doctor that you are taking GLUCOPHAGE (metformin hydrochloride tablets) when any new drug is prescribed or a change is made in how you take a drug already prescribed. GLUCOPHAGE may interfere with the way some drugs work and some drugs may interfere with the action of GLUCOPHAGE.

Q16. What if I become pregnant while taking GLUCOPHAGE?
Tell your doctor if you plan to become pregnant or have become pregnant. As with other oral glucose control medications, you should not take GLUCOPHAGE during pregnancy.

Usually your doctor will prescribe insulin while you are pregnant. As with all medications, you and your doctor should discuss the use of GLUCOPHAGE if you are nursing a child.

Q17. Are there other risks associated with GLUCOPHAGE?
There is some evidence that any oral diabetes drug may increase the risk of heart problems. Experts are not sure what the real risk is for heart problems, if any, from taking oral diabetes medicine.

Q18. How do I take GLUCOPHAGE?
Your doctor will tell you how many GLUCOPHAGE tablets to take and how often. This should also be printed on the label of your prescription. You will probably be started on a low dose of GLUCOPHAGE, and your dosage will be increased gradually until your blood sugar is controlled.

Q19. Where can I get more information about GLUCOPHAGE?
This leaflet is a summary of the most important information about GLUCOPHAGE. If you have any questions or problems, you should talk to your doctor or other healthcare provider about type 2 diabetes as well as GLUCOPHAGE and its side effects. There is also a leaflet (package insert) written for health professionals that your pharmacist can let you read.

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Bristol-Myers Squibb Company

Distributed by
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

Revised January 1999
60400IM 07

FS 8001R 1 99

FROM THE

New England Journal of Medicine

1996;334(9):574-579.

BAILEY CJ, TURNER RC: **METFORMIN.**

A comprehensive clinical review of GLUCOPHAGE® (metformin hydrochloride tablets) 500 mg

FS-A124

AN AUTHORITATIVE REVIEW FROM THE

NEW ENGLAND JOURNAL OF MEDICINE

USE OF GLUCOPHAGE IN FIRST-LINE AND COMBINATION THERAPY

MECHANISM OF ACTION

"[Metformin] improves insulin sensitivity and thus decreases the insulin resistance that is prevalent in NIDDM.*"

"...metformin has an antihyperglycemic action, whereas sulfonylureas and insulin have hypoglycemic actions."

EFFICACY

"[Metformin] can be used either as first-line therapy or in combination with a sulfonylurea."

"The efficacy of metformin in lowering blood glucose concentrations in obese and nonobese patients with NIDDM is similar to that achieved with a sulfonylurea."

SECONDARY BENEFITS

Unlike sulfonylureas:

"...metformin does not cause weight gain, reduces rather than increases plasma insulin concentrations, and rarely causes overt hypoglycemia."

Metformin also has a modest favorable effect on lipids.

SAFETY AND TOLERABILITY

"The rare but serious condition of lactic acidosis must be recognized as a potential adverse effect."

"...if metformin is avoided in patients with contraindications to its use, the drug is safe."

"Patients starting metformin therapy should be advised that they may have minor gastrointestinal side effects."

Please see full prescribing information, including the **boxed WARNING regarding Lactic Acidosis**, inside pocket.

*Non–insulin-dependent diabetes mellitus (type II).

Reprinted From

The New England Journal of Medicine

Established in 1812 as The NEW ENGLAND JOURNAL OF MEDICINE AND SURGERY

VOLUME 334 FEBRUARY 29, 1996 NUMBER 9

Original Articles

Images in Clinical Medicine

Editorials

Correspondence

SUMMARY

"...in Europe...[metformin] is used alone in approximately 40 percent of patients to whom it is prescribed and in combination with a sulfonylurea in approximately 60 percent."

"Metformin can be used either as initial therapy or as an additional drug when sulfonylurea therapy alone is inadequate."

WITH DIET—ALONE OR WITH A SULFONYLUREA

GLUCOPHAGE®

(METFORMIN HYDROCHLORIDE TABLETS) 500 mg

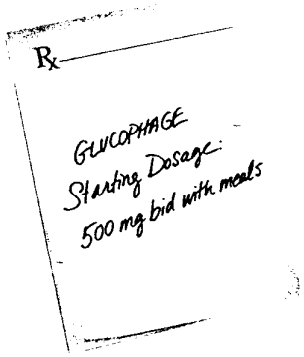
BOUND FOR EFFICACY AND SECONDARY BENEFITS

Highly effective first-line therapy

- Improves insulin sensitivity.[1]
- Does not produce hypoglycemia or hyperinsulinemia.[1]
- Helps keep weight from increasing and favorably affects lipids.[1]

Unique synergy in combination with a sulfonylurea

Provides a safety profile established in clinical use



Appropriate patient selection is key

- Rare occurrence of lactic acidosis, a serious condition.

  Approximately 0.03 cases per 1,000 patient-years reported worldwide. If it occurs, up to half may be fatal.

- Risk of lactic acidosis can be minimized by adhering to contraindications.

  Contraindicated in patients with renal disease or dysfunction and in patients with metabolic acidosis. *Temporarily* withhold in patients receiving parenteral iodinated contrast materials for radiologic studies. Avoid in patients with impaired hepatic function or excessive alcohol intake (acute or chronic).

Please see full prescribing information, including the **boxed WARNING regarding Lactic Acidosis**, inside pocket.

Reference: 1. Bailey CJ, Path MRC, Turner RC: Metformin. *N Engl J Med* 334(9):574-579, 1996.

MEDWatch 1-800-332-1088 available to report serious adverse events for any drug.

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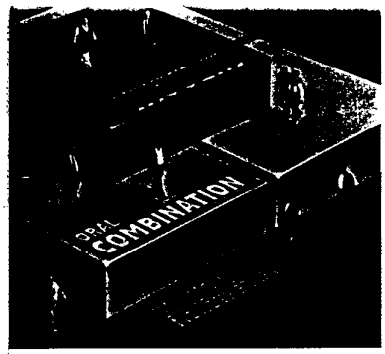
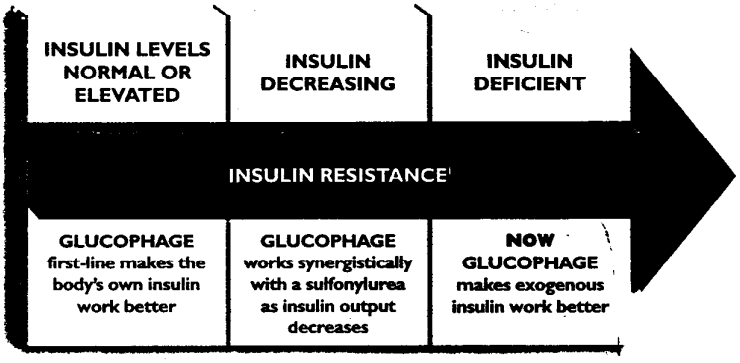


NOW FOR UNCONTROLLED TYPE 2 PATIENTS AT ANY STAGE



Adapted from DeFronzo.[1]

NEW INDICATION

Only GLUCOPHAGE provides all these benefits in combination with insulin

- **Improves glycemic control.**
- **Results in the need for less insulin.**
- **Maintains or reduces body weight.**

AS AN ADJUNCT TO DIET IN TYPE 2 DIABETES

GLUCOPHAGE®
(metformin hydrochloride tablets) 500 mg 1000 mg

Please see full prescribing information, including the **boxed WARNING regarding Lactic Acidosis.**

FRONT

FS-A267

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Reference: 1. DeFronzo RA: The triumvirate: β-cell, muscle, liver. A collusion responsible for NIDDM. *Diabetes* 37:667-687, 1988.

WHEN ORAL THERAPY IS NEEDED IN TYPE 2 DIABETES

GLUCOPHAGE®

(metformin hydrochloride tablets) 500 mg 1000 mg

Please see full prescribing information, including the **boxed WARNING regarding Lactic Acidosis.**

MEDWatch 1-800-332-1088 is available to report serious adverse events for any drug.

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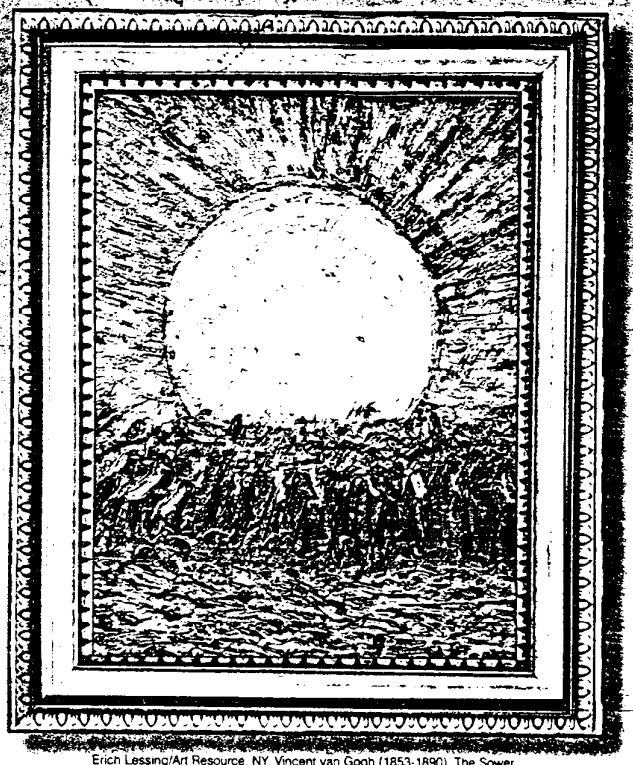
BACK

The Art of



Erich Lessing/Art Resource, NY. Vincent van Gogh (1853-1890). The Sower. Rijkmuseum Kroeller-Mueller, Otterlo, The Netherlands.

ACTIVITY

Erich Lessing/Art Resource, NY. Edgar Degas (1834-1917). Green Dancer. Fundacion Coleccion Thyssen-Bornemisza, Madrid, Spain.

FLEXIBILITY

In general, TAXOL is well tolerated. The most common adverse events associated with TAXOL are neutropenia, peripheral neuropathy, arthralgia/myalgia, and alopecia.

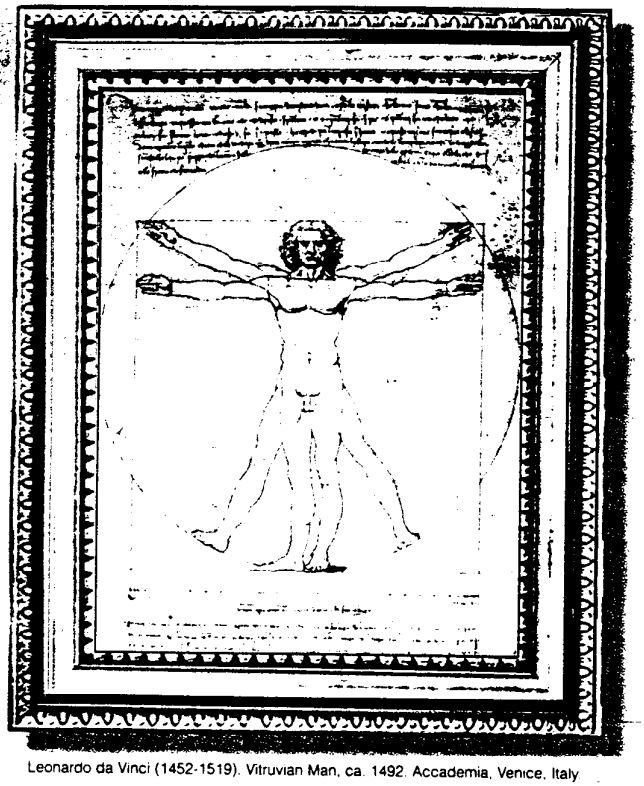
K4-K033R

*Please see adjacent pages for brief summary of prescribing information including indications, dosing, and administration.

†As of 1999.

‡TAXOL is a registered trademark of Bristol-Myers Squibb Company.

Versatility



Leonardo da Vinci (1452-1519). Vitruvian Man, ca. 1492. Accademia, Venice, Italy

Proven Activity

Flexible Dosing*

Validated Continually as a Single Agent and In Combination Within Cooperative Group Trials†

VALIDITY

SEMISYNTHETIC

TAXOL®‡

(paclitaxel) Injection

Clearly Versatile

BRISTOL-MYERS SQUIBB
ONCOLOGY

Bristol-Myers Squibb Company
Princeton, NJ 08543
U.S.A.

K4-K033E
6/99

K4-K032

The Art of VERSATILITY

Proven Activity

Flexible Dosing and Scheduling*

Validated Continually Within Cooperative Group Trials†

In general, TAXOL is well tolerated. The most common adverse events associated with TAXOL are neutropenia, peripheral neuropathy, arthralgia/myalgia, and alopecia.

*Please see adjacent pages for brief summary of prescribing information including indications, dosing, and administration.

†As of 1999.

‡TAXOL is a registered trademark of Bristol-Myers Squibb Company.

SEMISYNTHETIC

TAXOL®‡

(paclitaxel) Injection

Clearly Versatile

Scala/Art Resource, NY.
Michelangelo Buonarroti.
Creation of Adam; detail of the hands of God and Adam. Sistine Chapel, Vatican Palace, Vatican State.

BRISTOL-MYERS SQUIBB ONCOLOGY

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U.S.A.

K4-K032 6/99