The Journal of the American Diabetes Association

diabetes

CONTENTS

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INSULIN 50th ANNIVERSARY YEAR
1971-1972

When you prescribed Orinase®

(tolbutamide, Upjohn)

14 years ago, you had to rely on our experience.

An orally active hypoglycemic agent principally indicated in relatively mild, adult, maturity-onset, non-ketotic diabetes; also, as a supplement to insulin therapy in selected diabetic patients, it may effect a stabilization of labile diabetes and reduce insulin requirements. Certain patients intolerant to chlorpropamide therapy at usual therapeutic doses have subsequently been successfully managed with Orinase (tolbutamide).

Use in mild asymptomatic diabetic patients with abnormal glucose tolerance tests not responding to diet therapy may result in improvement of the glucose tolerance test.

Use in conjunction with phenformin is indicated when optimal control is not obtained with Orinase or phenformin alone.

Contraindications: Orinase alone is not effective in juvenile or growth-onset diabetes nor in unstable brittle diabetes where insulin therapy is required.

Orinase should not be used: when diabetes is complicated by acidosis, ketosis, or coma, or when a history of repeated bouts of acidosis or coma is obtained; in the presence of other acute complications such as fever, severe trauma, or infections; and in patients with severe renal insufficiency. Insulin is indicated in these circumstances.

Pregnancy Warning: The safety and usefulness of Orinase during pregnancy has not been established either from the standpoint of the mother or the fetus. Animal studies have demonstrated feticidal and teratogenic effects of doses of 1,000-2,500 mg./kg./day, but application to human subjects unknown. Therefore, Orinase is not recommended for the pregnant diabetic, and when administering Orinase to women of childbearing age, these facts should be borne in mind.

Precautions: Diagnostic and therapeutic measures necessary for optimal control with insulin are also necessary with Orinase. The patient on Orinase must be fully instructed: about the nature of his disease; how to prevent and detect complications; how to control his condition; not to neglect dietary restrictions, develop a careless attitude or disregard instructions relative to body weight, exercise, personal hygiene, and avoidance of infection; how to recognize and counteract impending hypoglycemia; how and when to test for glycosuria and ketonuria; how to use insulin; and to report to the physician immediately if he does not feel as well as usual.

Caution, very close observation, and careful adjustment of dose are necessary when: insulin is withdrawn during the trial period in order to avoid ketosis, acidosis, and coma; thiazide diuretics are administered which may result in aggravation of diabetic state and increased tolbutamide requirement, temporary loss of control, or even secondary failure; treating patients with impaired hepatic and/or renal function and debilitated, malnourished, or semistarved patients in order to avoid severe hypoglycemia which may require corrective therapy over several days; and treating patients with severe trauma, infection, or surgical procedures where temporary return to insulin or addition of insulin may be necessary. Response to tolbutamide is diminished in patients receiving therapy with beta blocking agents.

As some diabetics are not suitable candidates, it is essential that the physician familiarize himself with the indications, limits of application, and selection of patients for therapy.

Patients must be under continuous medical supervision, and during the initial test period should communicate with the physi-

Today you have your own.

If you're around 40 or 45, you've probably had quite a bit of clinical experience with Orinase.

Maybe as much as 14 years.

And that means you know quite a bit about it.

On the one hand, you know that diet and weight control are the initial and essential foundations for the management of adult-onset, non-ketotic diabetes. When these measures prove satisfactory, no additional therapy is indicated. On the other hand, you know that if these measures fail the addition of Orinase to the regimen can often help lower blood sugar. Orinase lowers blood sugar as effectively today as it did when you first prescribed it.

You also know the importance of close monitoring of the patient. Although uncommon, severe hypoglycemia may occur if the dosage is not tailored to suit his requirements.

In short, Orinase is a drug you're familiar with, and probably have confidence in.

And that may be the best recommendation Orinase can have.

Orinase®

0.5 g. tablets

(tolbutamide, Upjohn)

cian daily, and during the first month report at least once weekly for physical examination and definitive evaluation. After a month, examinations are recommended monthly or as indicated. Appearance of ketonuria, increase in glycosuria, unsatisfactory lowering or persistent elevation of blood sugar, or failure to obtain and hold clinical improvement indicate nonresponsiveness to Orinase (tolbutamide). Orinase does not obviate need for maintaining standard diet regulation. Uncooperative patients should be considered unsuitable for therapy. Prescriptions should be refilled only on specific instruction of physician. In treating mild asymptomatic diabetic patients with abnormal glucose tolerance, glucose tolerance tests should be obtained at three- to six-month intervals. Orinase is not an oral insulin or a substitute for insulin and must not be used as sole therapy in juvenile diabetes or in diabetes complicated by acidosis or coma where insulin is indispensable.

If phenformin is prescribed in combination with Orinase, appropriate package literature should be consulted.

Adverse Reactions: Severe hypoglycemia, though uncommon, may occur and may mimic acute neurologic disorders such as cerebral thrombosis. Certain factors such as hepatic and renal disease, malnutrition, advanced age, alcohol ingestion, and adrenal and pituitary insufficiency may predispose to hypoglycemia and certain drugs such as insulin, phenformin, sulfonamides, oxyphenbutazone, salicylates, probenecid, monamine oxidase inhibitors, phenylbutazone, bishydroxycoumarin, and phenyramidol may prolong or enhance the action of Orinase and increase risk of hypoglycemia. Orinase long-term therapy has been reported to cause reduction in RAI uptake without producing clinical hypothyroidism or thyroid enlargement and at high doses is mildly goitrogenic in animals. Photosensitivity reactions, disulfiram-like reactions after alcohol ingestion, and false-positive tests for urine albumin have been reported.

Although usually not serious, gastrointestinal disturbances (nausea, epigastric fullness, and heartburn) and headache appear to be dose related and frequently disappear with reduction of dose or administration with meals. Allergic skin reactions (pruritus, erythema, urticaria, and morbilliform or maculopapular eruptions) are transient, usually not serious, and frequently disappear with continued administration. Orinase should be discontinued if skin reactions persist. Recent reports indicate that long-term use of Orinase has no appreciable effect on body weight.

Orinase appears to be remarkably free from gross clinical toxicity: crystalluria or other renal abnormalities have not been observed; incidence of liver dysfunction is remarkably low and jaundice has been rare and cleared readily on discontinuation of drug (carcinoma of the pancreas or other biliary obstruction should be ruled out in persistent jaundice); leukopenia; agranulocytosis; thrombocytopenia; hemolytic anemia; aplastic anemia; pancytopenia; and hepatic porphyria and porphyria cutanea tarda have been reported.

Supplied: *0.5 g. Tablets*—bottles of 50, 200, 500, and 1,000, and cartons of 100 in foil strips.

For additional product information, see your Upjohn representative or consult the package insert.

The Upjohn Company, Kalamazoo, Michigan 49001 **Upjohn**

DIABETES®

The Journal of the American Diabetes Association

DIABETES is published by the American Diabetes Association, Inc., to provide an official Journal for the Association and to furnish the medical profession with information concerning diabetes and related fields of medicine.

Contributions are invited from practising physicians, clinical and laboratory investigators, and others who have data of importance to offer in these fields. Manuscripts, if suitable, will be accepted providing that the text has not been printed elsewhere.

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All signed articles and editorials are the responsibility of the author(s) and not that of the American Diabetes Association. The Editors will be pleased to consider for publication papers presented at the Annual Meeting of the Association. *Manuscript Specifications*: The length of manuscripts (not including special articles or letters) should be limited to 5,000 words, exclusive of illustrations, etc. Exceptions to this limitation will be made at the discretion of the Editors.

Communications for the "Brief Notes and Comments" department should not exceed 1,000 words except in unusual circumstances. Figures and tables in these brief communications should be limited to one of each, and references should not exceed twenty in number.

Manuscripts should be typewritten, with double spacing, and if possible, submitted in triplicate together with three copies of figures and photomicrographs.

References should be presented in the style of the following examples: For Periodicals—Banting, F. G.. and Best, C. H.: The internal secretion of the pancreas. J. Lab. Clin. Med. 7:251-66, Feb. 1922. For Books—Allen, Frederick M.: Studies Concerning Glycosuria and Diabetes. Cambridge, Harvard University Press, 1913, p. 461.

An abstract or summary of the content of the paper in not more than 250 words should usually appear at the beginning. This should be self-contained and understandable without reference to the text.

Photographs, drawings, and figures should be suitable for reproduction. Photographs should be unmounted, untrimmed glossy prints. The names of authors should appear on the back. The tops of photographs and figures should be indicated.

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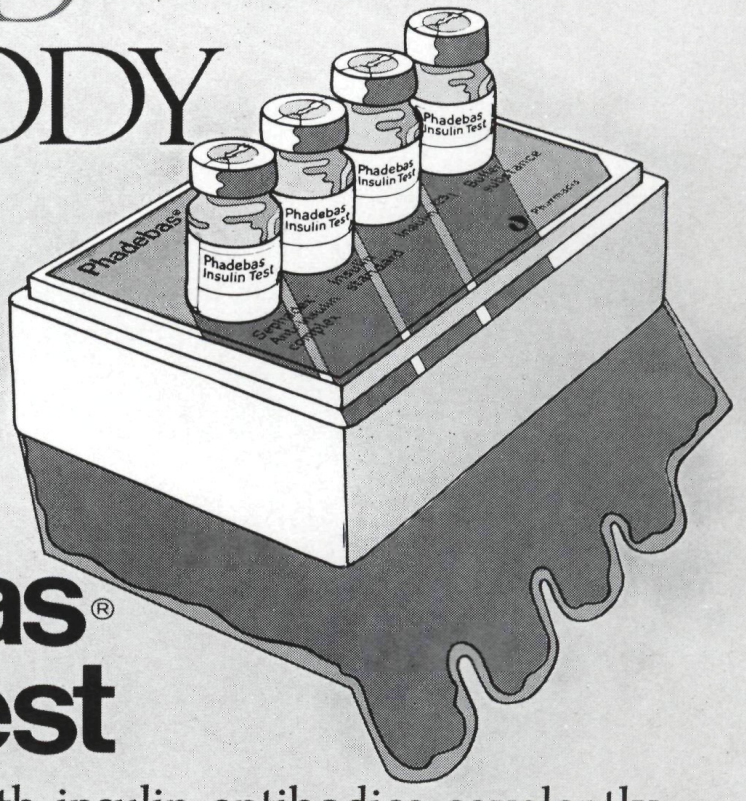

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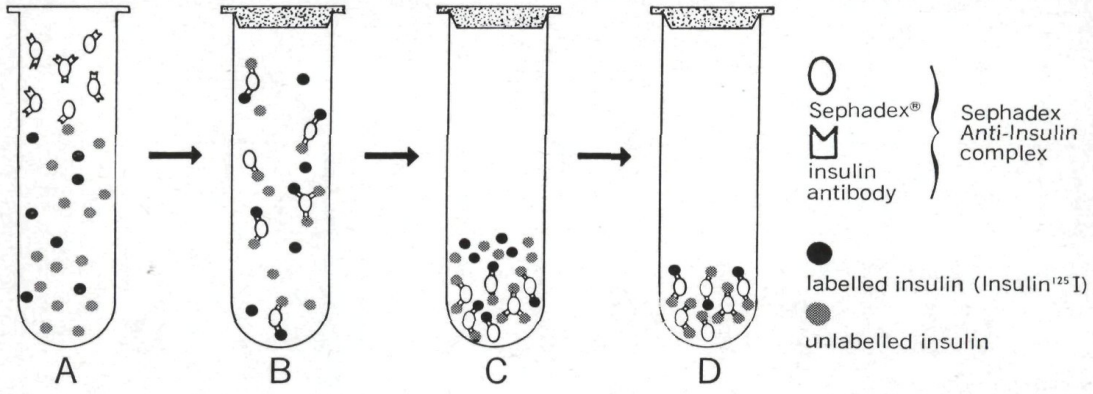

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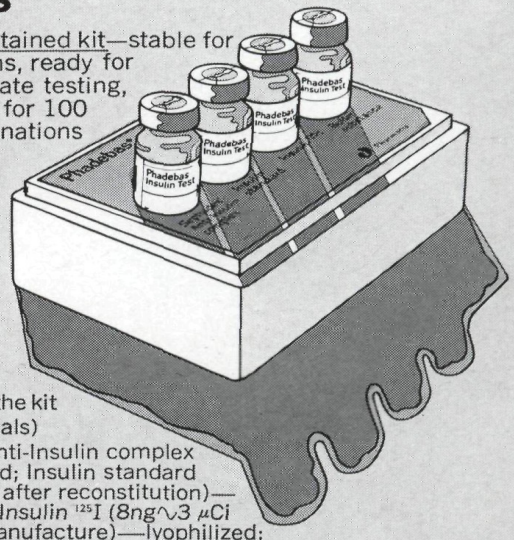

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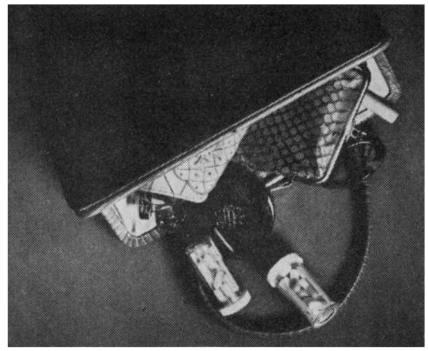
n oral hypoglycemic agent effective in ıe mild to moderately severe maturity-nset type of diabetes. Approximately ne third of failures to other ılfonylureas or to phenformin will ɜspond to Tolinase (tolazamide), lthough some of these patients will also ventually fail. Nonresponsive drug ɜilures may respond to combined olinase-phenformin therapy. Some ɑtients developing significant side ffects or intolerance to other oral drugs ıay be successfully maintained on olinase.

ls some diabetics are not suitable andidates for management with olinase, it is essential that physicians amiliarize themselves with the ndications, limits of application, and riteria for selection of patients for this herapy as described in the package nsert. Tolinase is not an oral insulin or nsulin substitute.

CONTRAINDICATIONS: Tolinase is not ndicated in diabetic patients who: are ɹndergoing surgery; have infections or severe trauma; have ketosis, acidosis or coma or history of repeated bouts of ɑcidosis and coma; or have juvenile or labile (brittle) diabetes. Tolinase is not recommended in patients with concurrent liver, renal, or endocrine disease and is contraindicated in uremia. Safety and usefulness during pregnancy have not been evaluated; therefore, Tolinase is not recommended in the pregnant diabetic patient. Serious consideration should be given to the potential hazards in women who might become pregnant.

PRECAUTIONS: Patients must be under continuous medical supervision particularly during the first six weeks of therapy. They should check their urines daily for sugar and acetone and should see their doctors at least once a week. Diagnostic and therapeutic measures necessary for optimal control with insulin and other sulfonylureas are also necessary with Tolinase. The patient must receive complete instructions: about the nature of his disease; how to prevent and detect complications; how to control his condition; not to neglect



dietary restrictions or develop a careless attitude regarding instructions relative to body weight, exercise, and personal hygiene; to avoid infections; how to recognize and counteract impending hypoglycemia; and how and when to test for glycosuria and ketonuria. No false positive tests for urinary albumin have been reported.

Caution, close observation, and careful adjustment of dose are necessary: when insulin is withdrawn during the trial period where the appearance of acidosis, ketosis, or coma would make the discontinuation of Tolinase (tolazamide) and return to insulin therapy mandatory; when Tolinase is administered as sole therapy to patients previously receiving combination therapy; during the transition period from chlorpropamide to avoid overlapping drug effect and possible hypoglycemia; in administering thiazide-type diuretics which may aggravate diabetes; and in debilitated, malnourished, semistarved patients or those not eating properly who may develop severe hypoglycemic reactions requiring corrective therapy. Severe hypoglycemia, though uncommon, may occur and may mimic acute neurologic disorders. Certain conditions such as hepatic and renal disease, malnutrition, debility, advanced age, alcoholism, and adrenal and pituitary insufficiency may predispose to hypoglycemia. Certain drugs such as insulin, phenformin, sulfonamides, oxyphenbutazone, phenylbutazone, salicylates, probenecid, and monamine oxidase inhibitors may increase the risk of hypoglycemia. When combination therapy with phenformin is elected, the physician should familiarize himself with the prescribing information for that drug.

ADVERSE REACTIONS: Tolinase has been generally well tolerated. In 1,784 diabetic subjects, 2.1% had therapy discontinued because of side effects. The following adverse reactions have been reported either during clinical studies or subsequently.

Gastrointestinal—Symptoms including nausea, vomiting, and gas were noted in 1% of patients in clinical studies.

Hematopoietic—Rare cases of leukopenia, thrombocytopenia, agranulocytosis, and anemia have been reported.

Hypoglycemia—Hypoglycemia has been reported occasionally and is actually a physiological extension of the primary action of the drug, and most of the mild to moderately severe symptoms will be alleviated by dose reduction. Undernourished or underweight or geriatric patients, or those failing to eat properly are particularly susceptible to hypoglycemia and should be treated cautiously. Patients with chronic liver or kidney disease should not receive Tolinase (tolazamide) therapy as their metabolism or excretion of drug may be poor and they may be more susceptible to hypoglycemia.

Liver—Toxicity manifested by changes in liver function tests and by cholestatic jaundice has been occasionally associated with Tolinase therapy. Transient elevations in alkaline phosphatase determinations are not uncommon after initiation of sulfonylureas, but these changes are not necessarily drug related since fluctuating abnormalities of hepatic function are frequently observed in diabetic patients.

Skin—Allergic reactions as manifested by urticaria and rash have been reported occasionally. Photosensitivity and disulfiram reactions with alcohol have been reported occasionally.

Miscellaneous—Symptoms of weakness, fatigue, dizziness, vertigo, malaise, and headache were reported infrequently but relationship to therapy was difficult to assess.

SUPPLIED: *100 mg* Scored Tablets—bottles of 100. *250 mg* Scored Tablets—bottles of 100, 200, and 1,000 and cartons of 100 tablets in foil strips.

For additional product information, see package insert or consult your Upjohn representative.

The Upjohn Company
Kalamazoo, Michigan 49001

Upjohn

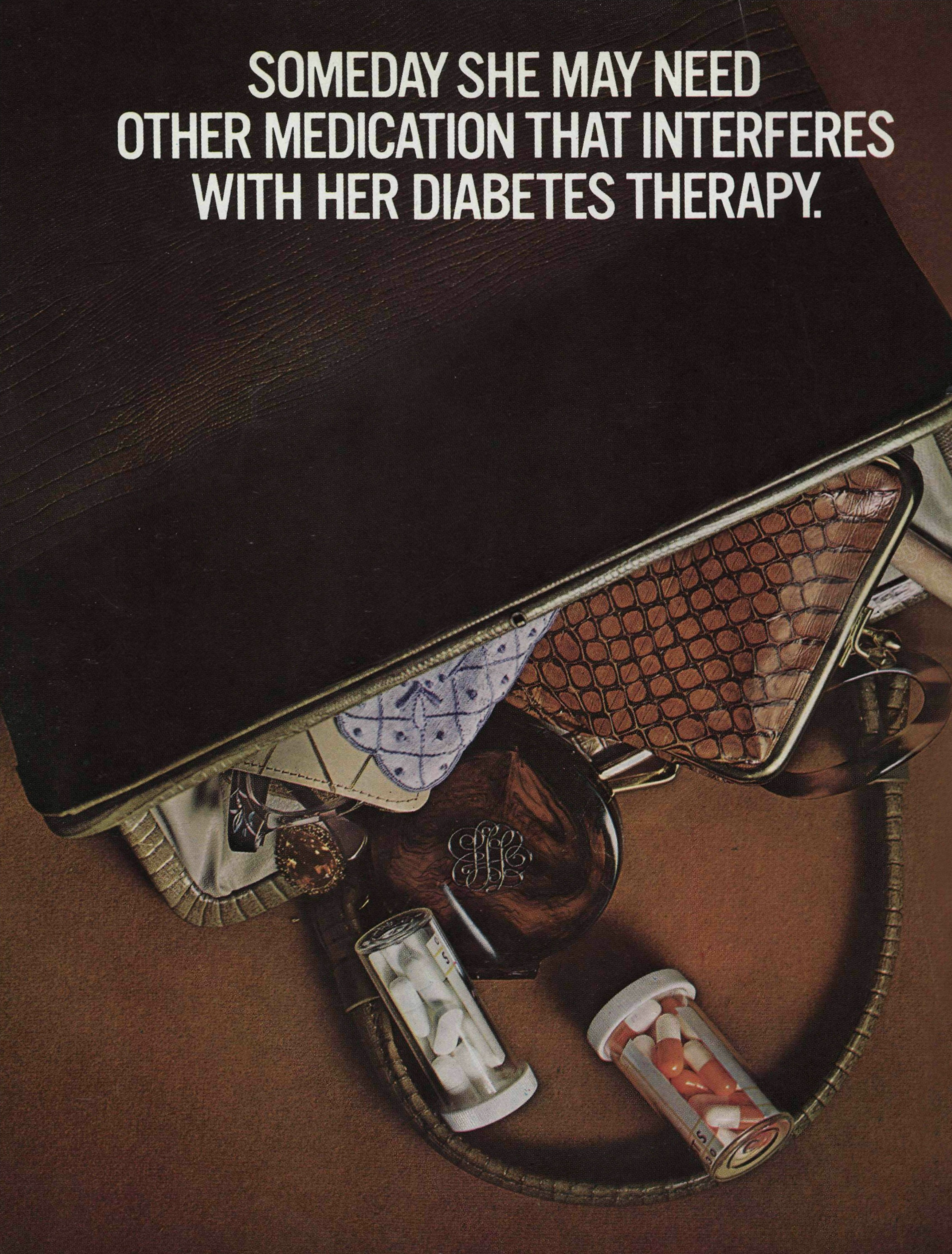
MED B-7-S (KRM-11) JA71-1395

250 MG TABLETS

TOLINASE®

(tolazamide, Upjohn)

IT GIVES YOU ROOM TO REACT


SOMEDAY SHE MAY NEED
OTHER MEDICATION THAT INTERFERES
WITH HER DIABETES THERAPY.

SOMETHING TO CONSIDER IN SELECTING AN ORAL HYPOGLYCEMIC DRUG.

Let's say you have a stable maturity-onset diabetic patient. You've been trying to control her blood-sugar level through a program of diet and weight loss alone, but it has not proved satisfactory. You decide to add an oral hypoglycemic drug to her therapy. What other considerations are involved before you decide *which* oral hypoglycemic drug to choose?

One of the things you may consider is that someday that same patient might have to take a sulfonamide or a thiazide, or a salicylate, or some other drug that will affect the action of the oral hypoglycemic drug. So whatever oral drug you choose should allow you maximum room to adjust and compensate for the added medication.

Tolinase (tolazamide, Upjohn) could be your best choice.

Tolinase dosage flexibility allows you to adapt readily to the addition of other drugs. A number of drugs are known to prolong or enhance the action of Tolinase, which means in many cases you'll have to adjust the Tolinase dosage downward. Among those drugs are insulin, phenformin, sulfonamides, oxyphenbutazone, phenylbutazone, salicylates, probenecid, and monamine oxidase inhibitors. On the other hand, the addition of thiazide-type diuretics or chlorpromazine to a patient's therapy can elevate blood sugar and make it necessary to increase the sulfonylurea dosage.

Either way, Tolinase offers the necessary dosage flexibility to react. It has the widest range of usable potency of any of the sulfonylureas: from 50 mg to 1,000 mg, in 50 mg increments (using 100 mg scored tablets). That's 20 steps from low to high—more room to react than any other sulfonylurea offers you.

Once-a-day dosage...your patient has less to forget because she has less to remember. Once-a-day dosage at breakfast provides satisfactory blood-sugar control for most responsive patients. This feature may be particularly important to patients who are taking other medications in addition to Tolinase. The fewer pills they have to remember—and take—in any one day, the less they may forget.

For those few patients who may require more than 500 mg of Tolinase daily, however, the dosage should be divided. Alterations in liver function tests have been occasionally associated with Tolinase therapy.

Your Upjohn representative has more to tell. He'll be happy to discuss all the other important features of Tolinase with you—both pharmacologic and clinical.

For further prescribing information, see first page of this advertisement.

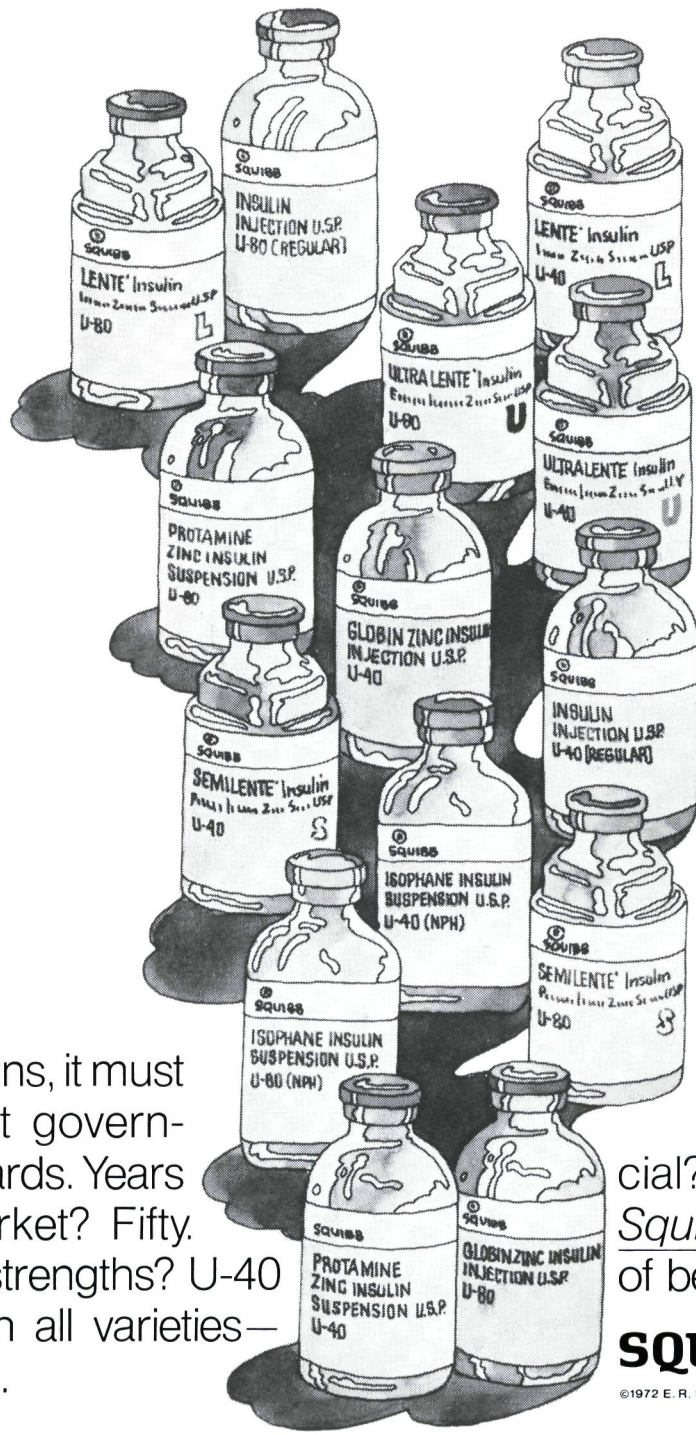
250 MG. TABLETS

TOLINASE®

(tolazamide, Upjohn)

IT GIVES YOU ROOM TO REACT

Have you considered 'the other' insulin, Doctor?



Like all insulins, it must satisfy strict government standards. Years on the market? Fifty. Types and strengths? U-40 and U-80 in all varieties—even Globin.

So what makes 'the other' insulin so special? *Squibb quality and Squibb price*—that's our way of becoming "the" insulin.

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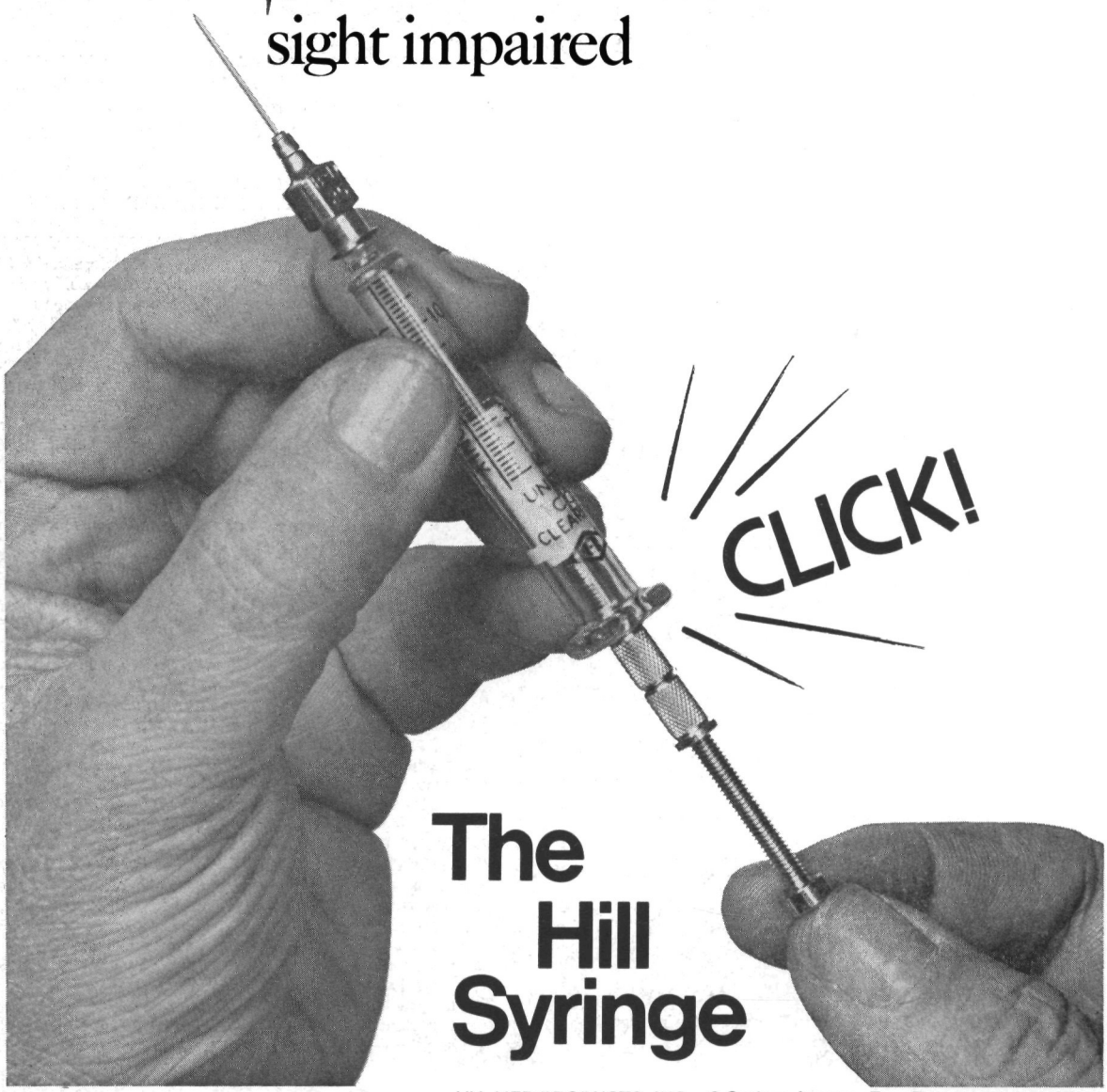
59% of diabetics make dosage errors / Insure patient confidence /
Ideal for the blind and infirmed / Eliminates confusion as to dosage / Consistency of dosage /
Psychological patient acceptance / Controlled results / Economical to use

exact every time for the diabetic.

sight impaired



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