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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, complications, and necessary personal measures needed to maintain control of the disease.

Caution: Very close observation, and careful adjustment of dose are necessary when: insulin is withdrawn during the trial period in order to avoid ketosis, acidosis, and coma; thiazide diuretics are administered, since they may aggravate the diabetic state and increase 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 to avoid severe hypoglycemia; and treating patients with severe trauma, infection, or surgical procedures where temporary return to insulin or addition of insulin may be necessary. Beta-blocking agents reduce response to tolbutamide.

Patients must be under continuous medical supervision, and during the initial test period should communicate with the physician 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. Ketonuria, increased glycosuria, unsatisfactory lowering or persistent elevation of blood sugar, or poor clinical response indicate nonresponsiveness to *Orinase*. *Orinase* does not obviate the need for maintaining standard diet regulation. In treating mild asymptomatic diabetic patients with abnormal glucose tolerance, glucose tolerance tests should be obtained at 3-6 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.

***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. Certain drugs such as insulin, sulfonamides, oxyphenbutazone, salicylates, probenecid, monamine oxidase inhibitors, phenylbutazone, bishydroxycoumarin, and phenylhydrazol may prolong or enhance the action of *Orinase* (tolbutamide) and increase risk of hypoglycemia. *Orinase* long-term therapy has been reported to reduce RAI uptake without producing clinical hypothyroidism or thyroid enlargement. High doses are 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. Reports indicate that long-term use of *Orinase* has no appreciable effect on body weight.

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