Revised: May 2013 (7th version)

Standard Commodity Classification No. of Japan
873961

- ORAL HYPOGLYCEMIC AGENT -

DEAMELIN®·S Tablets 250 mg

< Glyclopyramide tablet>

Powerful drug and Prescription drug Note)

Storage
This product should be stored at room temperature.
Expiration date
This product should be used before the expiration date indicated on the outer cases.

Approval No.	21900AMX01734000
Date of listing in the NHI reimbursement price	December 2007
Date of initial marketing in Japan	November 1965
Date of latest reevaluation	March 1993

Note) Caution: Use only as directed by a physician

WARNINGS

This product may induce a serious and prolonged hypoglycemia. Read the sections of "DOSAGE AND ADMINISTRATION" and "PRECAUTIONS" carefully before use of this product.

CONTRAINDICATIONS (This product is contraindicated in the following patients.)

(1) Patients with severe ketosis, diabetic coma or precoma, and insulin-dependant diabetes [Insulin must be applied.]
(2) Patients with serious hepatic or renal dysfunction [Hypoglycemia may occur.]
(3) Patients with severe infections, pre- or post-operation, and serious injury [Insulin must be applied.]
(4) Patients with gastrointestinal disorders, such as diarrhea and vomiting [Hypoglycemia may occur.]
(5) Patients with a history of hypersensitivity to any of ingredients of this product or sulfonamide preparations
(6) Pregnant or possibly pregnant women (See the section of "Use during Pregnancy, Delivery or Lactation.")

DESCRIPTION

Product description

Ingredient/content per tablet	Glyclopyramide 250 mg			
Inactive ingredients	Crystalline cellulose, lactose hydrate, carmellose calcium, potato starch, magnesium stearate			
Dosage form	Plain			
Color	White			
Appearance	KP 105 			
	13.0 mm in long diameter	5.5 mm in short diameter	4.2 mm in thickness	About 325 mg in weight
Identification code	KP-105			

INDICATIONS

Insulin-independent diabetes mellitus (when symptoms cannot be managed by diet and exercise alone)

DOSAGE AND ADMINISTRATION

The usual dosage of this product for oral use is 125 to 250 mg of Glyclopyramide daily, and as required, may be increased to determine a maintenance dose, with the upper limit of 500 mg daily.

This product should be orally administered once daily before or after breakfast, or twice daily before or after breakfast and supper.

PRECAUTIONS

1. Careful Administration (This product should be administered with care in the following patients.)

(1) Patients with hepatic or renal dysfunction
(2) Patients with a possible episode of hypoglycemia, or the following conditions
 1) Hepatic or renal dysfunction
 2) Pituitary malfunction or adrenal insufficiency
 3) Malnutrition, starvation, irregular intakes of meals, and shortage of dietary intake or debility
 4) Heavy muscular exercise
 5) Excessive alcohol intake
 6) Elderly patients (See the section of "Use in the Elderly.")
 7) Coadministration of this product with a drug enhancing hypoglycemia, as shown in the section of "Drug Interactions"

2.Important Precautions

(1) This product should be administered to just the patients with an established diagnosis of diabetes. Attention should be paid to the diseases showing diabetes-like symptoms (e.g., renal glycosuria, geriatric oligosaccharidoses and thyroid dysfunction), such as abnormal glucose tolerance and positive glycosuria.
(2) This product should be administered only after diet and exercise therapies failed to manage diabetes properly.
(3) Administration of this product should be started at a low dose, and the clinical response be investigated by regular examinations for blood and urine sugar, with the doses gradually increased. If the response is poor, this product should be immediately switched with another therapy.

(4) Since the cases in which administration may not be required, the dose must be reduced, or little or no clinical response may be induced by noncompliance with treatment of patients or complicated infections may occur during the period of treatment, attention should be paid to dietary intake, change in body weight, blood glucose and the presence or absence of infections to judge continuation of administration, dosage, and selection of drugs.

(5) Since this product may cause **serious and prolonged hypoglycemia**, patients should be cautioned against engaging in potentially hazardous activities requiring alertness, such as operating machines, working in heights, or driving cars. In addition, the patients and their families should be adequately informed of precautions concerning hypoglycemia.

3. Drug Interactions

Precautions for Coadministration (This product should be administered with care when coadministered with the following drugs.)

(1) Drugs enhancing hypoglycemic action

1) Signs and symptoms

Hypoglycemic symptoms, such as weakness, highly hungry feeling, diaphoresis, palpitation, tremor, headache, sensory abnormality, anxiety, excitement, nervousness, decreased mental concentration, mental disorder, disturbed consciousness, and convulsions may develop owing to an increase in hypoglycemic action.

2) Treatment

When this product is coadministered with any of the following drugs, patients' conditions should be adequately monitored including plasma glucose and the dosage of this product or coadministered drug should be adjusted with care if necessary. If any of hypoglycemic symptoms is observed, sucrose should be usually administered. **Separately, if any of hypoglycemic symptoms is observed by coadministration of the product with an α-glucosidase inhibitor (acarbose or voglibose, etc.), glucose should be administered.**

3) Mechanism and Risk Factors

Drugs	Mechanism and Risk Factors
Insulin product	Plasma insulin is increased.
Biguanide-type drugs	Gluconeogenesis in the liver and absorption of glucose from the gut are reduced.
Drugs improving insulin sensitivity: Troglitazone	Insulin action is enhanced.
α-Glucosidase inhibitors: Acarbose, Voglibose, etc.	Absorption of glucose is reduced.
DPP-4 inhibitors: Sitagliptin phosphate hydrate, Vildagliptin, etc. GLP-1 receptor agonists: Liraglutide	Insulin secretion may be accelerated and glucagon secretion may be inhibited.
Probenecid	Renal excretion of this product is delayed.
Coumarin anticoagulants: Warfarin potassium	Metabolism of this product in the liver is inhibited.
Salicylates: Aspirin, etc.	Binding of this product to plasma protein is inhibited. Salicylates have hypoglycemic effects.
Pyrazolone-type antiinflammatory drugs: Ketophenylbutazone, etc.	Binding of this product to plasma protein is inhibited, and its renal excretion is delayed.
β-Blockers: Propranolol hydrochloride, etc.	Gluconeogenesis and recovery from hypoglycemia due to adrenaline are suppressed, and sympathetic symptoms resulting from hypoglycemia are masked.
Monoamine oxidizing-enzyme inhibitors	Gluconeogenesis is suppressed, and insulin secretion is accelerated.
Sulfonamides	Binding of this product to plasma protein and metabolism in the liver are inhibited, and its renal excretion is delayed.
Chloramphenicol	Metabolism of this product in the liver is inhibited.
Tetracycline antibiotics	Sensitivity to insulin in the peripheral tissues is enhanced.
Fibrate-type drugs: Clofibrate, Bezafibrate, etc.	Binding of this product to plasma protein and metabolism in the liver are inhibited, and its renal excretion is delayed.
Guanethidine sulfate	Catecholamine in the tissues may be exhausted, although the mechanism remains unknown.
Miconazole, Fluconazole	Metabolism of this product in the liver is inhibited.

(2) Drugs reducing hypoglycemic action

1) Signs and symptoms

Hyperglycemic symptoms, such as nausea, vomiting, dehydration, and acetone smell in exhalation may develop owing to a decrease in hypoglycemic action.

2) Treatment

When this product is coadministered with any of the following drugs, patients' conditions should be adequately monitored including plasma glucose.

3) Mechanism and Risk Factors

Drugs	Mechanism and Risk Factors
Adrenaline	Glucose intake in the peripheral tissues is suppressed, and gluconeogenesis in the liver is accelerated.
Adrenocortical hormone	Gluconeogenesis in the liver is accelerated, and sensitivity to insulin in the peripheral tissues is reduced.
Thyroid hormone	Absorption of glucose from the gut and secretion of glucagon are accelerated, and the effects of catecholamine, and gluconeogenesis in the liver are enhanced.
Follicular hormone	Cortisol secretion, sugar availability in the tissues and hepatic function are changed, and growth hormone is excessively produced, although the mechanism remains unknown.
Diuretics: Thiazides, Chlorthalidone, Ethacrynic acid, Acetazolamide, Triamterene, Furosemide, etc.	Insulin sensitivity of the peripheral tissues is reduced and secretion of insulin is suppressed.
Pyrazinamide	Control of plasma glucose levels has been reported to be difficult, although the mechanism remains unknown.
Isoniazid	Metabolism of glucose is damaged,

	and an increase in plasma glucose levels, and abnormal glucose tolerance are induced.
Rifampicin	Metabolism of this product in the liver is enhanced.
Nicotinic acid	Anabolism of glucose in the liver is inhibited.
Phenothiazines	Insulin secretion is inhibited, and epinephrine is released from the adrenal glands.
Phenytoin	Insulin secretion is inhibited.
Buserelin acetate	Administration of this drug to diabetic patients has been reported to induce change in the diabetic type from insulin-independent to insulin-dependent, although the mechanism remains unknown.

4. Adverse Reactions

This product has not been investigated (Drug-use results surveys, etc.) to determine the incidence of adverse reactions. The incidence data on the product have therefore been collected from investigations until approval and the literature.

Out of a total of 975 cases, 53 cases (5.44%) had adverse reactions (including laboratory test abnormalities). The most common reactions included 23 events (2.36%) of hypoglycemia, eight (0.82%) of anorexia, and four (0.41%) each of abdominal discomfort, increased AST (GOT) and increased ALT (GPT) (the results of reevaluation).

Adverse reactions with their incidences unknown are also included in the following data.

(1) Clinically significant adverse reactions

1) Hypoglycemia (2.36%)

Weakness, heavy hungry feeling, diaphoresis, palpitation, tremor, headache, sensory abnormality, anxiety, excitement, nervousness, decreased mental concentration, mental disorder, disturbed consciousness, and/or convulsions may occur. If such a symptom occur, administration should be discontinued with appropriate therapeutic measures taken. Since mental disorder and disturbed consciousness may mainly develop when hypoglycemia deteriorates gradually, attention should be paid to such a case.

As appropriate measures of hypoglycemia, sucrose should be usually given after administration of this product alone, and glucose after coadministration of this product with an α-glucosidase inhibitor (acarbose or voglibose, etc.).

2) Aplastic anemia and agranulocytosis (incidence unknown)

Since aplastic anemia and agranulocytosis may occur, patients should be adequately monitored. If such an abnormality is observed, administration should be discontinued with appropriate measures taken.

(2) Other Adverse Reactions

	0.1≤ <5%	**Incidence unknown**
Hematologic		Thrombocytopenia
Hepatic	Hepatic dysfunction	Hepatic porphyria
Gastrointestinal	Abdominal discomfort, etc.	
Hypersensitivity	Rash, photosensitivity	
Others	Headache	Lowered alcohol tolerance, abnormal thyroid function

5. Use in the Elderly

This product should be administered to elderly patients with care for hypoglycemia, with a low starting dose and frequent monitorings.

[Since elderly patients often have reduced physiological functions, hypoglycemia may frequently occur.]

6. Use during Pregnancy, Delivery or Lactation

(1) This product should not be administered to pregnant or possibly pregnant women.

[Sulfonylurea preparations have been reported to cross the placenta to induce hypoglycemia in newborns and macrosomia.]

(2) Use of this product is not recommended in lactating women.

[Other sulfonylurea preparations have been reported to be excreted in the breast milk.]

7. Overdosage

(1) Signs or symptoms:

Overdosage of this product may induce hypoglycemia. (See the heading of "Hypoglycemia" in the section of "Adverse Reactions.")

(2) Treatment:

1) For the patients who can ingest food, in general, sucrose should be orally given after administration of this product, and glucose after coadministration of this product with an α-glucosidase inhibitor (acarbose or voglibose, etc.).

2) For the patients with disturbed consciousness, 20 mL of a 50% glucose solution should be intravenously administered, and as required, a 5% glucose solution should be instilled to retain euglycemia.

3) Glucagon may also be administered as a hyperglycemic hormone.

8. Precautions Concerning Use

Precautions regarding dispensing: For the drug that is dispensed in a press-through package (PTP), patients should be instructed to remove the drug from the package prior to use.

[It has been reported that if the PTP sheet is swallowed, its sharp corners may puncture the esophageal mucosa, resulting in serious complications such as mediastinitis.)

9. Other Precautions

(1) It has been reported that a long-term use of a sulfonylurea preparation (tolbutamide at a daily dose of 1.5 g) induced significantly higher mortality from cardiovascular disorder as compared with a diet therapy alone.

(2) It has been reported that administration of an angiotensin converting enzyme inhibitor is likely to induce hypogly-

cemia during treatment with insulin or an oral hypoglycemic drug.

PHARMACOKINETICS

1. Plasma Concentrations[1)]

When a tablet of this product was orally given to male beagle dogs, the plasma concentrations reached the peak of 70.7 μg/mL after 3.3 hours, with the biological half-life of 4.0 hours.

2. Metabolism and Excretion[2)]

When Glyclopyramide at a single dose of 11 mg/body was orally given to rats, the major metabolite excreted in urine within 24 hours was the unchanged form, and an excretion ratio of the form to its metabolite p-chlorobenzenesulfonamide was 27:1. The ratio in bile, however, was 2.5:1. N-acetyl-p-chlorobenzenesulfonamide was also excreted as a minor metabolite. Overall, the metabolites including the unchanged form were mainly excreted in the urine, and the amount excreted in both urine and feces within 24 hours accounted for 80% of the dose.

PHARMACOLOGY

When Glyclopyramide at a dose of 150 mg/kg was orally given to rabbits, the time to reach the peak of the plasma concentrations coincided with that to reach trough of the glucose levels, with about 1 hour after dosing. In addition, a dose response of Glyclopyramide at doses of 12.5 to 100 mg in rats was linear at 1 hour, and the hypoglycemic effect was 2.66 times as high as that of tolbutamide.[3),4)]

PHYSICOCHEMISTRY

Nonproprietary name:

Glyclopyramide (JAN)

Chemical name:

N-(p-Chlorobenzenesulfonyl)-N'-pyrrolidinourea

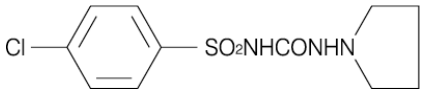
Molecular formula:

$C_{11}H_{14}ClN_3O_3S$

Molecular weight:

303.77

Structural formula:



Melting point:

195 to 200 ºC

Description:

Glyclopyramide occurs as a white crystalline powder, with no odor. It is soluble in dimethylformamide, slightly soluble in acetone and chloroform, and practically insoluble in water, ethanol (95%), and diethylether.

It is soluble in sodium hydroxide and ammonia solutions.

Partition coefficient:

Organic phase	Water phase	Partition coefficient
Chloroform	Britton-Robinson buffer at pH 6.9	3.99

At 25ºC

PACKAGING

DEAMELIN·S Tablets 250 mg

100 tablets (10 tablets x 10), 500 tablets (10 tablets x 50) and 1000 tablets (10 tablets x 100) in press-through packages

REFERENCES

1) Uchida H., Comparative absorption study of glyclopyramide preparations (In-house data)
2) Abe Y. et al., *The Clinical Report*, 11, 1639 (1977)
3) Oda T. et al., *The Journal of Therapy*, 47, 843 (1965)
4) Irikura T. et al., *J. Pharmaceutical Soc. Jpn*., 85, 104 (1965)

REQUEST FOR LITERATURE SHOULD BE MADE TO:

A request for in-house data mentioned in the References can also be made to the following.

Kyorin Pharmaceutical Co, Ltd. Drug Information Center
6, Kanda surugadai 4-chome, Chiyoda-ku, Tokyo 101-8311, Japan
TEL: 0120-409-341 (Toll-free)
9:00 to 17:30 (Monday through Friday exclusive of national holidays)

Manufactured and Marketed by:

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