Revised: September 2009 (7th version, revision associated with the Pharmaceutical Affairs Law (abolition of the term of "Designated drug", etc.)
Revised: February 2008

Improving Agent for Cerebral Circulation and Metabolism

NICERGOLINE TABLETS 5mg "TOWA"

Storage:
Store at room temperature.
Expiration date:
Indicated on the package and label

Standard Commodity Classification No. of Japan 87219	
Approval No.	21800AMX10498
Date of listing in the NHI reimbursement price	December 2006
Date of initial marketing in Japan	July 2000

* Caution - Use only pursuant to the prescription of a physician, etc.

CONTRAINDICATIONS (Nicergoline Tablets is contraindicated in the following patients.)

Patients in whom hemostasis after intracranial hemorrhage appears to be incomplete [Hemorrhage may be aggravated.]

DESCRIPTION

Active ingredient per tablet	Nicergoline (JP) ····· 5 mg		
Inactive ingredient	Lactose Hydrate, D-Mannitol, Partly Pregelatinized Starch, Hydroxypropylcellulose, Ethylcellulose, Magnesium Stearate, Hypromellose, Macrogol 6000, Talc, Titanium Oxide		
Product description	White film-coated tablets		
Identification code	Tablet	Tw CE	
	Package		
Appearance	Top surface	Bottom surface	Side surface
			
Diameter (mm)	6.2		
Thickness (mm)	3.0		
Weight (mg)	85		

INDICATIONS

Improvement of hypobulia due to chronic cerebral circulatory disorder resulting from sequelae of cerebral infarction

DOSAGE AND ADMINISTRATION

The usual adult dosage for oral use is 15mg of nicergoline daily in 3 divided doses. The dosage may be adjusted according to the patient's age and symptoms.

PRECAUTIONS FOR DOSAGE AND ADMINISTRATION

The duration of treatment with nicergoline should be determined after careful consideration of clinical response and the severity of adverse reactions. For patients showing no response at Week 12 of treatment, nicergoline administration should be discontinued.

PRECAUTIONS

1. Adverse Reactions

No investigation such as a drug use investigation clearly showing the incidence of adverse reactions has been conducted.

If any of the following adverse reactions is observed, appropriate measures such as discontinuing administration should be taken.

	Incidence unknown
Gastrointestinal	Anorexia, diarrhea, constipation , nausea, abdominal pain, thirst
Hepatic	Abnormal hepatic function
Cardiovascular	Dizziness, postural dizziness, palpitations, hot flush
Psychoneurologic	Sleepiness, malaise, headache, tinnitus, insomnia
Hypersensitivity	Rash, urticaria, pruritus

2. Use in the Elderly

Since elderly patients often have reduced physiological functions, careful supervision and measures such as reducing the dosage are recommended.

3. Use during Pregnancy, Delivery or Lactation

1) This product should be used in pregnant women or in women who may possibly be pregnant only if the expected therapeutic benefits outweigh the possible risks associated with treatment. [In animal studies (in rats), developmental delay has been reported in the next generation.]
2) It is recommended that nicergoline administration to nursing women be avoided; however, if it is considered essential, breast-feeding should be suspended. [In animal studies (in rats), nicergoline has been reported to be excreted in breast milk.]

4. Pediatric Use

The safety in children, etc. has not been established.
(No clinical experience)

5. Precautions Concerning Use

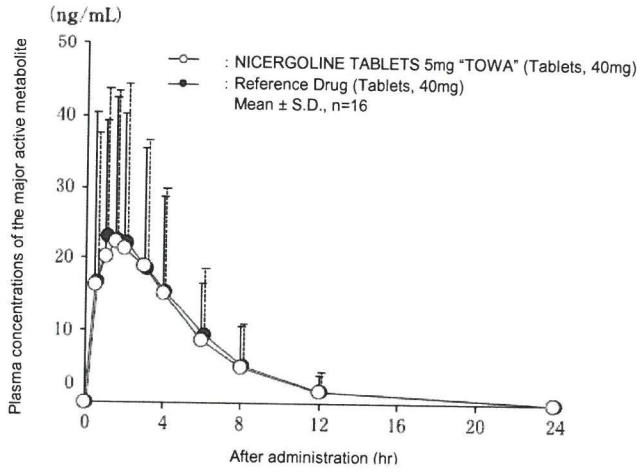
Precautions regarding dispensing:
For drugs that are dispensed in a PTP (press-through package) sheet, instruct the patient to remove the drug from the package prior to use [It has been reported that, if the PTP sheet is swallowed, the sharp corners of the sheet may puncture the esophageal mucosa, causing perforation and resulting in severe complications such as mediastinitis.]

PHARMACOKINETICS

1. Bioequivalence test

In a cross-over study, single doses of 8 tablets of Nicergoline Tablets 5mg "TOWA" and 8 tablets of a reference drug (equivalent to 40 mg of nicergoline) were orally administered to healthy adult men (n = 16) under fasting conditions; plasma concentrations of the major active metabolite of 10-methoxy-1, 6-dimethylergoline-8 β-methanol were measured and data obtained on pharmacokinetic parameters (AUC, Cmax) were

statistically analyzed. The analysis results confirmed the bioequivalence of these drugs (based on PAB Notification No. 718 dated May 30, 1980).[1)]
(Note) Oral administration of nicergoline 40 mg in a single dose is beyond the approved dosage of Nicergoline Tablets 5 mg "TOWA".



	Determined parameter		Reference parameter	
	AUC_{24} (ng·hr/mL)	Cmax (ng/mL)	Tmax (hr)	$T_{1/2}$ (hr)
NICERGOLINE TABLETS 5mg "TOWA" (Tablets, 40mg)	133.01±123.13	28.48±23.77	1.25±0.98	2.57±0.69
Reference drug (Tablets, 40mg)	137.85±135.39	28.25±24.87	1.47±0.94	2.88±0.83

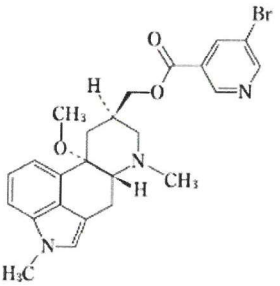
(Mean ± S.D., n=16)

Plasma concentration and parameters such as AUC and Cmax may differ according to study conditions such as selection of subjects and frequency/time of body fluid sample collection.

2. Dissolution profile
Nicergoline Tablets 5mg "TOWA" has been confirmed to conform to the corresponding dissolution standards of Nicergoline tablets defined in the third section of the Japanese Pharmaceutical Codex[2)].

PHYSICOCHEMISTRY

Structural formula:



Nonproprietary name:
Nicergoline
Chemical name:
[(8*R*, 10*S*)-10-Methoxy-1, 6- dimethylergolin-8-yl] methyl 5-bromopyridine-3-carboxylate
Molecular formula:
$C_{24}H_{26}BrN_3O_3$
Molecular weight:
484.39
Description:
Nicergoline occurs as white to light yellow, crystals or crystalline powder. It is soluble in acetonitrile, in ethanol (99.5) and in acetic anhydride, and practically insoluble in water. It is gradually colored to light brown by light.
Melting point:
About 136°C (with decomposition)

PRECAUTIONS FOR HANDLING

Stability test
In an accelerated test using final packaged products (at 40°C and 75% relative humidity for 6 months), NICERGOLINE TABLETS 5mg "TOWA" were estimated to be stable for 3 years under normal distribution conditions[6)]

PACKAGING

NICERGOLINE TABLETS 5mg "TOWA":
Boxes of 100 tablets, 1,000 tablets (PTP)
Polyethylene containers of 1,000 tablets

REFERENCES

1) Internal data of Towa Pharmaceutical Co., Ltd.: Bioequivalence test
2) Internal data of Towa Pharmaceutical Co., Ltd.: Dissolution test
3) Internal data of Towa Pharmaceutical Co., Ltd.: Stability test

Manufacturer and Distributor
TOWA PHARMACEUTICAL CO., LTD.
2-11, Shinbashi-cho, Kadoma, Osaka 571-8580
Japan