037523-2

Japan standard product classification number 871139•871179

*Revised in March 2020
Revised in October 2021 (22nd edition)

Storage method: Tablets: Store at room temperature Fine grains: Moisture-proof, store at room temperature

Expiration date: Use within the expiration date indicated on the package.

Use as soon as possible after opening, even if the expiration date has not passed.

Prescription drugs **for psychoactive epilepsy and mania** (Caution - Use only with a doctor's prescription)

テグレトール®錠100mg
テグレトール®錠200mg
テグレトール®細粒50%
Tegretol®

Carbamazepine preparations

Approval number	Tablet 100mg: 20300AMZ00826000 Tablet 200mg: 20300AMZ00827000 Fine grain 50%: 21500AMZ00527000		
	Tablet 100mg	Tablet 200mg	Fine granules
50% NHI drug price listing	July 1992	July 1992	July 2004
Sales start	July 1992	March 1966	March 1969
Re-evaluation results	–	June 1975	
additional indication		March 1990	

SUN PHARMA

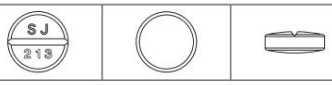
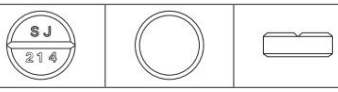
ÿ **[Contraindications (Do not administer to the following patients)]** Patients with a history of hypersensitivity to the components of this drug or tricyclic antidepressants1 Patients with serious blood disorders [Hematologic disorders may occur as a side effect] 2 have been reported, and there is a risk of further worsening blood abnormalities.]

3. Patients with grade II or higher atrioventricular block or severe bradycardia (less than 50 beats/min) [Stimulus conduction may be suppressed and even more severe atrioventricular block may occur.]

If you are currently taking voriconazole, tadalafil (Adcirca), ril-4pivirine, macitentan, ticagrelor, grazoprevir, elbasvir, daclatasvir/asunaprevir/beclabvir, asunaprevir, dolutegravir/rilpivirine, sofosbuvir/velpatasvir, bictegravir/emtricitabine/tenofovir alafenamide. Patients [Blood concentrations of these drugs may decrease.]] (See section 3. Interactions) 5. Patients with porphyria [Porphyrin synthesis increases,

Symptoms may worsen.]

ÿComposition•Characterÿ

Tegretol tablets 100mg	Ingredients and Contents	1 Tablet of ÿÿÿÿÿÿÿ (Japanese version) 100ÿ
	Additives	Hydroxypropyl cellulose, corn starch, cellulose, magnesium stearate
	Properties: White uncoated tablet with score line on one side	
	shape	
	Identification code	SJ 213
	Size (approx.)	Diameter: 8.0 mm Thickness: 2.9 mm Mass: 0.14 g
Tegretol tablets 200mg	Ingredients/Content	1 tablet Carbamazepine (Japanese
	Additives	Pharmacopoeia) 200 mg Hydroxypropyl cellulose, corn starch, cellulose, magnesium stearate
	Properties: White uncoated tablet with score line on one side	
	shape	
	Identification code	SJ 214
	Size (approx.)	Diameter: 9.0 mm Thickness: 3.7 mm Mass: 0.28 g
Tegretol fine grain 50%	Ingredients/Content	Carbamazepine (JP) 500 mg in 1 g Corn
	Additives	starch, povidone, silicic anhydride
	Properties	White fine grains

[Efficacy or effect]

1. Psychomotor seizures, epileptic personality and mental disorders associated with epilepsy, epileptic seizures: tonic-clonic seizures (generalized seizures, grand mal seizu

2. Mania, manic state in manic-depressive disorder, excited state in schizophrenia 3. Trigeminal neuralgia

[Usage and dosage]

1. For psychomotor seizures, epileptic personality and mental disorders associated with epilepsy, epileptic seizures: tonic-clonic seizures (generalized seizures, grand mal seizures) As carbamazepine, the initial daily dose for adults is 200 to 400 mg. Administer orally in 1 to 2 divided doses and gradually increase the dose until the optimal effect is achieved (usually 600 mg per day). The dose can be increased to 1,200 mg per day depending on symptoms. For children, 100 to 600 mg per day is usually administered orally in divided doses, depending on age and symp

2. For mania, manic state of manic-depressive disorder, and excited state of schizophrenia For adults, the usual daily dose of carbamazepine is 200 to 400 mg orally administered in 1 to 2 divided doses to achieve the optimal effect. Gradually increase the dose until the drug is completely absorbed (usually 600 mg per day). The dose can be increased to 1,200 mg per day depending on symptoms.

3. For trigeminal neuralgia

Carbamazepine is usually administered orally to adults at a daily dose of 200 to 400 mg, usually up to 600 mg per day, but the dose can be increased to 800 mg per day depending on the symptoms. For children, reduce the dose as appropriate depending on age and symptoms.

[Precautions for use]

1. Careful administration (Administer with caution to the following patients) (1) Patients with heart disease such as heart failure, myocardial infarction, or first-degree atrioventricular block [This drug may suppress impulse conduction and worsen cardiac function. There is.]

(2) Patients who have difficulty urinating or increased intraocular pressure [symptoms may worsen as it has anticholinergic effects].] (3) Elderly (see section 5. Administration in the Elderly) (4) Patients with liver or kidney disorders [These patients have decreased metabolic and excretory functions, so blood Administer carefully by monitoring intermediate concentrations.]

(5) Patients with drug hypersensitivity (6) Patients with hypothyroidism [lower thyroid hormone concentration] There are reports that.]

2. Important basic precautions

(1) A sudden decrease in dosage or discontinuation of administration during prolonged use may cause status epilepticus, so if discontinuing administration, gradually reduce the dose. Please do so carefully.

Please be especially careful if you are elderly or infirm.

(2) It is recommended to perform liver/kidney function and blood tests periodically during continuous use.
Yes.

(3) As drowsiness and a decrease in alertness, concentration, and reflex motor ability may occur, patients receiving this drug should be careful not to engage in dangerous activities such as driving a car. . (4) When used to treat the excited state of schizophrenia, it should be used when antipsychotic drugs are not sufficiently effective. (5) Seizures may be exacerbated or induced by administration of antiepileptic drugs. When administering this drug to patients with mixed seizure type or small seizures for which this drug is considered ineffective (absence seizures, atypical absence seizures, atonic seizures, myoclonic seizures), pay attention to the condition and monitor the seizures. If symptoms worsen or are induced, gradually reduce the dose of this drug and discontinue it.

(6) Symptoms such as drowsiness, nausea/vomiting, dizziness, double vision, and ataxia are often signs of overdosage, so if such symptoms occur, take up to the optimal effective dose. Reduce weight gradually. It is particularly common in the early stages of administration, so it is desirable to start administration at a lower dose.

ÿ **3. Interaction**

Interactions of this drug with many drugs have been reported, but not all possible combinations have been investigated, so do not use this drug concomitantly with other drugs, or discontinue this drug or concomitant drugs. Be careful in this case. In particular, the main metabolic enzyme of this drug is cytochrome P450 3A4, and it also induces metabolic enzymes including cytochrome P450 3A4, so when used in combination with drugs that affect these activities or are metabolized by them, be careful. The drug should be administered carefully by measuring blood drug concentrations and observing clinical symptoms as much as possible, and paying attention to the dose. In addition, the enzyme involved in the metabolism of carbamazepine-10, 11-epoxide, the main metabolite of carbamazepine, is epoxide hydrolase, and when used in combination with a drug that inhibits this enzyme, carbamazepine-10, 11- Since the blood concentration of epoxide may increase, clinical symptoms should be observed as much as possible and the dose should be carefully administrated.

(1) Concomitant use contraindications (do not use together)

Drug name, etc.	Clinical symptoms/measures	Mechanism/risk factors
Voriconazole (Vifend) Tadalafil (Adcirca) Rilpivirine (Edulant) Macitentan (Opsumit) Tikagrelor (Brilinta) Grazoprevir (Gradyna) Elbasvir (Elersa) Daclatasvir Asunaprevir Bec Rabvir (Zimency) Asunaprevir (Sunvepra) Dolutegravir Rilpivirine (Jalka)	There is a risk that the blood concentration of these drugs will decrease and their effects will be weakened.	The metabolic enzyme inducing effect of this drug accelerates the metabolism of these drugs.
Sofosbuvir velpatasvir (Epclusa)		Due to the inducing effect of this drug on P-gp and metabolic enzymes, the plasma concentrations of these drugs may decrease.
Bictegravir emtricitabine tenofovir arafe namide (Biktarvy)	Decreased plasma concentrations of bictegravir and tenofovir alafenamide may reduce the effectiveness of this drug and may lead to the development of resistance to this drug.	This is due to the P-gp and metabolic enzyme inducing effect of this drug.

(2) Caution when using concomitant use (Be careful when using concomitantly)

Drug name, etc.	Clinical symptoms/measures	Mechanism/risk factors
MAO inhibitor	There is a risk that their mutual effects may be enhanced.	Interactions between tricyclic antidepressants and MAO inhibitors have been reported, and as this drug has a similar structure to tricyclic antidepressants, similar symptoms may occur.
Lithium Carbonate	There have been reports of neuropsychiatric symptoms (confusion, mechanism unknown; gross tremor, disorientation, etc.).	
Metoclopramide	There have been reports of neurological symptoms (gait disturbance, mechanism unknown; ataxia, nystagmus, diplopia, hyperreflexia of the lower extremities).	
alcohol	There is a risk that their mutual effects may be enhanced. Avoid excessive alcohol consumption.	Both have central nervous system depressant effects.
Central nervous system depressants Haloperidol Thioridazine	Mutual effects may be enhanced.	
Diuretics (sodium-losing)	Hyponatremia/ SIADH may appear. Consider using a non-sodium-losing diuretic.	Both may lower serum sodium.
Isoniazid	Hepatotoxicity of isoniazid This drug may enhance its metabolic enzyme-inducing effects. In addition, the metabolism of the blood concentration of this drug is accelerated, liver toxicity rapidly increases, and toxic isoniazid symptoms (drowsiness, nausea, vomiting, vomiting, vomiting, vomiting, etc.) It will be rough. Also, it may be damaged. Azide inhibits the metabolism of this drug, increasing the blood concentration of this drug.	
Fluvoxamine Verapamil Diltiazem Cimetidine Omeprazole Danazol Bicalutamide Quinupristin/Dalfopristin Macrolide antibiotics Erythromycin Clarithromycin, etc. Ritonavir Darunavir Azole antifungals Miconazole Fluconazole, etc. Ciprofloxacin	The blood concentration of this drug may rise rapidly, and symptoms of toxicity (drowsiness, nausea/vomiting, dizziness, etc.) may occur.	These drugs inhibit the metabolism of this drug, increasing the blood concentration of this drug.
Acetazolamide		The mechanism is unknown.
Quetiapine	The blood concentration of quetiapine may decrease. Additionally, the blood concentration of this drug's metabolites may increase.	The metabolic enzyme inducing effect of this drug accelerates the metabolism of quetiapine and lowers its blood concentration. In addition, quetiapine inhibits the metabolism of this drug's metabolites, increasing the blood concentration of this drug's metabolites.
itraconazole telaprevir	Blood levels of these drugs may decrease. Additionally, the blood concentration of this drug may increase.	The metabolic enzyme inducing effect of this drug accelerates the metabolism of these drugs and lowers their blood concentrations. In addition, these drugs inhibit the metabolism of this drug, increasing the blood concentration of this drug.
clobazam paroxetine		The metabolic enzyme inducing effect of this drug accelerates the metabolism of these drugs and lowers their blood concentrations. The mechanism by which the blood concentration of this drug increases is unknown.

Drug name, etc.	Clinical symptoms/measures	Mechanism/risk factors
Phenobarbital Rifampicin	The blood concentration of this drug may decrease.	The metabolic enzyme-inducing effects of these drugs accelerate the metabolism of this drug, and the blood concentration of this drug decreases.
Phenytoin	Blood concentration of this drug decreases.	Both drugs may induce metabolic enzymes. In addition, because it has the action of phenytoin, it promotes the metabolism of phasephenytoin in the blood, increasing or decreasing its concentration in the blood, thereby decreasing its concentration in the blood. There is something. Additionally, due to metabolic competition, phenytoin metabolism may be inhibited, resulting in increased blood levels of phenytoin.
Valproic acid	May decrease blood concentration of valproic acid. Additionally, the blood concentration of this drug and its metabolites may increase or the blood concentration of this drug may decrease.	The metabolism of valproic acid is promoted by the metabolic enzyme inducing effect of this drug. Additionally, valproic acid inhibits the metabolism of this drug's metabolites. There are reports that the blood concentration of this drug increases or decreases when used in combination with valproic acid, but the mechanism is unknown.
Primidone	Blood concentrations may decrease mutually. Additionally, the blood concentration of this drug's metabolites may increase.	It is thought that the metabolic enzyme inducing effects of both drugs mutually promote metabolism. Primidone also inhibits the metabolism of this drug's metabolites, increasing the blood concentration of this drug's metabolites.
Efavirenz	Blood concentrations may decrease with each other.	It is thought that the metabolic enzyme inducing effects of both drugs mutually promote metabolism.
Theophylline Aminophylline		The metabolism of theophylline is promoted by the metabolic enzyme inducing effect of this drug. Additionally, there are reports that the blood concentration of this drug decreases and the half-life of this drug decreases when used in combination.
Anxiety / Sleeping agent Al Prazolum Midazolam anti -Japanese antepsy agent Zonisamide chronazepam otoscimid Topillamid Panel Panel Panel Panel -doll Buprenolphin anti -Parkinson agent Itra Defilin Buchirofenon -based psycho -neurological agent Halopedol, etc. Lamin Amitripricin Nort Reciputirin, etc. Tradon Mianzerin Coloralin Melta Pin Psychiatric nerves Medications Olanzapine Aripiprazole Risperidone Blonanserin Clozapine Paliperidone Donepezil Flecainide Eletriptan Dihydropyridine Calcium antagonists Nifedipine Felodipine Nilvadipine, etc. Ondansetron Corticosteroids Prednisolone Dexamethasone, etc.	It may reduce the effects of these drugs.	The metabolic enzyme inducing effect of this drug accelerates the metabolism of these drugs and lowers their blood concentrations.

Drug name, etc.	Clinical symptoms/measures	Mechanism/risk factors
Luteal /follicular hormones Drospirenone/ Ethinylestradiol, etc.	There is a risk of decreased efficacy and increased incidence of abnormal vaginal bleeding.	The metabolic enzyme inducing effect of this drug accelerates the metabolism of these drugs and lowers their blood concentrations.
Solifenacin Coumarin anticoagulant Warfarin Immunosuppressant Cyclosporin Tacrolimus Everolimus Antineoplastic agent Irinotecan Imatinib Gefitinib Sorafenib Sunitinib Dasatinib Nilotinib Lapatinib Toremifene Tamibarotene Temsirolimus Axitinib Ceritinib Osimertinib Palbociclib Ibrutinib ponatinib	It may reduce the effects of these drugs.	
Anti-cancer drug lenvatinib		Due to the inducing effect of this drug on P-gp and metabolic enzymes, the blood concentration of lenvatinib may decrease.
Doxycycline antiviral agent (HIV infection treatment drugs) Saquinavir Indinavir Nelfinavir Lopinavir Dolutegravir/ Abacavir/Lami Vudine, etc. Maraviroc Delavirdine Etravirine Praziquantel Eplerenone Sildenafil Tadalafil (Cialis) Dienogest Aprepitant Rivaroxaban Simvastatin		The metabolic enzyme inducing effect of this drug accelerates the metabolism of these drugs and lowers their blood concentrations.
fosaprepitan tomeglumine		The metabolic enzyme inducing effect of this drug accelerates the metabolism of aprepitant, the active form of fosaprepitant meglumine, and lowers its blood concentration.
Digoxin Non-depolarizing muscle relaxants Pancuronium etc. Albendazole		The mechanism is unknown.
Hydroxychloroquine	The effect of this drug may be reduced.	
Acetaminophen	May reduce the effect of acetaminophen. There are also reports that it increases the likelihood of liver damage.	The metabolic enzyme inducing effect of this drug accelerates the metabolism of acetaminophen and lowers its blood concentration. It also accelerates the metabolism of acetaminophen to N-acetyl-p-benzoquinoneimine, which is hepatotoxic .
lamotrigine	It may decrease the blood concentration of lamotrigine.	Glucuronidation of lamotrigine in the liver is promoted.

Drug name, clinical symptoms, countermeasures , mechanism,		
dabigatrane texilate	It may reduce the effect of dabigatran.	**risk factors** Due to the P-glycoprotein inducing effect of this drug, the blood concentration of dabigatran may decrease.
Foods containing St. John's Wort	Be careful not to ingest foods containing St. John's wort when administering this drug, as the metabolism of this drug may be accelerated and the blood concentration may decrease.	Metabolic enzymes induced by St. John's wort are thought to promote the metabolism of this drug.
grapefruit juice	Be careful not to ingest grapefruit juice when administering this drug, as the metabolism of this drug may be suppressed and the blood concentration may increase.	It is thought that the ingredients contained in grapefruit juice suppress the enzymes that metabolize this drug in the small intestine, increasing its blood concentration.
Mirabegron	The action of mirabegron may be attenuated.	Due to the metabolic enzyme inducing effect and P-glycoprotein inducing effect of this drug, the metabolism of mirabegron is accelerated and its blood concentration decreases.
Cyclophosphamide	May enhance the effects of cyclophosphamide.	Due to the metabolic enzyme inducing effect of this drug, the concentration of active metabolites of cyclophosphamide increases.
Caspofungin	The blood concentration of caspofungin may decrease.	This drug affects the uptake and transport process of caspofungin, leading to the induction of caspofungin clearance.

4. Side

effects 1,282 side effects were observed in 614 (38.1%) of the 1,613 cases investigated, and the main symptoms were drowsiness in 223 cases (13.8%), dizziness in 146 cases (9.1%), and light-headedness in 137 cases (8.5%), malaise/feeling of fatigue 56 (3.5%), ataxia 56 (3.5%), weakness 50 (3.1%), rash 46 (2.9%), headache/dull head 43 (2.7%). %), dizziness on standing up (40 cases (2.5%)), and dry mouth (34 cases (2.1%)). (Up to approval of additional indications, approval of additional dosage forms, and tabulation of literature) In addition, abnormal clinical test values included ÿ-GTP increase in 18.1% (53/293) and AST (GOT) increase in 4.5% (15/335).), ALT (GPT) increased in 7.7% (26/336), ALP increased in 5.5% (18/325), and white blood cell count decreased in 3.7% (12/321).

(Tally up to the time of additional indication approval)

ÿ **(1) Serious side effects 1) Aplastic anemia, pancytopenia, leukopenia, agranulocytosis, anemia, hemolytic anemia, erythroblastic aplasia, thrombocytopenia (incidence unknown): Serious blood disorders** This may occur, so monitor the patient carefully by conducting periodic blood tests, and if any abnormalities are found, discontinue administration and take appropriate measures.

2) **Toxic Epidermal Necrolysis: TEN), mucocutaneous ocular syndrome (Stevens Johnson syndrome), erythema multiforme, acute generalized exanthematous pustulosis, erythroderma (exfoliative dermatitis) (incidence unknown): Serious** skin symptoms may occur, so carefully monitor If abnormalities such as fever, eye redness, swelling of the face, erosion of the lips/oral mucosa or genital area, blisters on the skin or mucous membranes, numerous small pustules, erythema, sore throat, itching, or general malaise are observed. Immediately discontinue administration and take appropriate measures.

In addition, most of these symptoms occur within 3 months of starting administration of this drug, so patients should be carefully monitored, especially during the early stages of administration.

3) SLE-like symptoms (incidence unknown): SLE-like symptoms (skin symptoms such as butterfly erythema, fever, arthralgia, white blood cell count, thrombocytopenia, anti-nuclear antibody positivity, etc.) may occur, so be sure to monitor the patient carefully. If any abnormalities are observed, administration should be discontinued and appropriate measures should be taken. 4) Hypersensitivity syndrome (incidence unknown): Initial symptoms include fever and rash, and further symptoms include lymphadenopathy, arthralgia, increased white blood cells, eosinophilia, appearance of atypical lymphocytes, hepatosplenomegaly, and liver dysfunction. Delayed serious hypersensitivity symptoms accompanied by organ damage may occur. Also, be aware that **symptoms such as rash, fever, and liver dysfunction may flare up or become prolonged .** In addition, it is often **accompanied by reactivation of viruses such as** human herpesvirus 6 (HHV-6). If such symptoms occur, administration should be discontinued and appropriate measures should be taken. 5) Hepatic dysfunction, jaundice (incidence unknown): Cholestatic, hepatocellular , **mixed, or granulomatous liver dysfunction and jaundice may occur, which may lead to fulminant hepatitis, etc., so** Patients should be carefully monitored, including liver function tests. If any abnormalities are observed, administration should be discontinued and appropriate measures should be taken. **6) Acute kidney injury (interstitial nephritis, etc.) (incidence unknown): Serious** kidney injury may occur, so patients should be carefully monitored by regularly conducting kidney function tests, and if any abnormality is detected. If this occurs, administration should be discontinued and app

7) PIE syndrome, interstitial pneumonia (incidence unknown): PIE syndrome and interstitial pneumonia accompanied by fever, cough, dyspnea, sputum, eosinophilia, and infiltrative shadows in the lung fields may occur. If such symptoms occur, administration should be discontinued and appropriate measures should be taken. 8) Thromboembolism (incidence unknown): Thromboembolism such as pulmonary embolism, deep vein thrombosis, and thrombophlebitis may occur, so carefully observe the patient and take appropriate action if any abnormality is observed. Discontinue administration and take appropriate measures. 9) Anaphylaxis (incidence unknown): Anaphylaxis accompanied by urticaria, angioedema, circulatory failure, hypotension, dyspnea, etc. may occur. If such symptoms occur, discontinue administration and take appropriate precautions. To carry out Do treatment.

10) Congestive heart failure, atrioventricular block, sinus insufficiency, bradycardia (incidence unknown): Congestive heart failure, atrioventricular block, sinus insufficiency, bradycardia may occur, so patients should be carefully observed to detect any abnormalities. If observed, administration should be discontinued and appropriate measures should be taken. **11) Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) (incidence** unknown): Incompatibility with antidiuretic hormone accompanied by hyponatremia, hypoosmolaremia, increased urinary sodium excretion, hypertonic urine, convulsions, impaired consciousness, etc. Secretory syndrome (SIADH) may occur. If such symptoms occur, administration should be discontinued and appropriate measures such as restricting fluid intake should be taken. 12) Aseptic meningitis (incidence unknown): Aseptic meningitis may be accompanied by stiff neck, fever, headache, nausea/vomiting, or clouded consciousness, so if such symptoms occur, If so, discontinue administration and take appropriate measures. 13) Malignant syndrome (incidence unknown): Administration of this drug may cause fever, impaired consciousness, akinesi

Tachycardia, blood pressure fluctuations, sweating, etc. may occur. In such cases, administration should be discontinued and appropriate measures should be taken along with systemic management such as body cooling and hydration. This may occur if the drug is abruptly discontinued, so do not abruptly discontinue administration of this drug. In addition, special care should be taken as malignant syndrome is more likely to occur when used in combination with antipsychotic drugs. Furthermore, at the onset of this disease, an increase in white blood cells and serum CK (CPK) are often observed, and a decline in renal function accompanied by myoglobinuria may be observed.

(2) Other side effects

	Frequency unknown	5% or more	0.1% to less than 5%	Less than 0.1%
Note 1) Difficult	Vasculitis, angioedema, dyspnea, allergies		Scarlet fever-like/ measles-like/toxic eruption, urticarial rash, eruption, flushing, pruritus	Photosensitivity
skin	Pigmentation, acne, papules, erythema multiforme nodularis, purpura, hirsutism, lichenoid keratosis, nail disorders (onycholysis, nail deformation, nail discoloration, etc.)			
Musculoskeletal	system—		Muscle weakness	Muscle spasm, joint pain, myalgia
Blood Note 1)	Porphyria, megaloblastic anemia, leukocytosis, eosinophilia, reticulocytosis		lymphadenopathy	
Liver Note 1)	—	ALL (GPT), Increase in ALP, ÿ-GTP increase	ASTÿGOTÿ	
kidney	Lack of urine, anuria, hematuria		Proteinuria, BUN, frequent urination Increased creatinine	
mental nervous system	Hallucinations (visual vision, light-headedness, sleep, attention/concentration, confusion, hearing), dizziness, dizziness, delirium, abnormal sensations, decreased ability, dizziness, impotence, peripheral neuritis, depression , dystonia, heaviness of the head, weakness, nervousness, chore malaise, athetosis, tremor, ataxia, paralytic symptoms, involuntary movements, aggressive behavior, tremor (tremor, dystonia, disturbance of consciousness, laxity) etc.), sedation, memory impairment, language impairment, harm		headache/orofacial	
Eye Note 2)	Abnormal eye movements (eye roll attacks), lens opacity, conjunctivitis, increased intraocular pressure		Double vision, blurred vision, accommodation disorder,	nystagmus
cardiovascular system	Arrhythmia, stimulating conduction disorders		Blood pressure decrease	Blood pressure increase
digester	Erythritis Note 1), intrastomatitis , glossitis, abdominal pain, colitis		Anorexia, nausea/ vomiting, constipation, diarrhea, dry mouth	
Department of Endocrinology and Metabolism	Abnormal vitamin D/ calcium metabolism (low serum calcium, etc.), abnormal thyroid function test values (low T4 levels, etc.), low serum folate levels, gynecomastia, galactorrhea, elevated prolactin, hyponatremia, osteomalacia, osteoporosis, hyperglycemia			
others	Hearing abnormalities (tinnitus, hyperacusis, hearing loss, change in pitch, etc.), hair loss, increased cholesterol, increased triglyceride, CK (CPK) increase, fluid retention, immunoglobulin decrease (IgA, IgG, etc.), CRP increase		Fever, dysgeusia, common cold-like symptoms, edema, symptoms (nasopharyngeal sweat, weight gain,	cephalitis, cough, etc.)

Note 1) If symptoms appear, administration should be discontinued.
Note 2) It is desirable to conduct visual acuity tests regularly.

5. Administration to the

elderly: In general, elderly people have decreased physiological functions, so care should be taken to reduce the dose.

6. Administration to pregnant women, parturient

women, lactating women, etc. (1) The drug should be administered to pregnant women or women who may be pregnant only when the therapeutic benefits are judged to outweigh the risks. . If it is unavoidable to administer this drug during pregnancy, it is desirable to avoid concomitant use with other antiepileptic drugs as much as possible. [There are reports from epidemiological studies that many patients who received this drug during pregnancy gave birth to children with malformations (including spina bifida) or children with developmental disabilities. 1) In addition, compared to administering this drug alone , the combination of this drug and other antiepileptic drugs (particularly sodium valproate) has been associated with a higher incidence of births of infants with malformations such as cleft palate, cleft lip, and ventricular septal defect. There is an epidemiological survey report that shows that there are many . 2) There are also reports of hypospadias .]

(2) It has been reported that if this drug is used in combination with this drug or other anti-epileptic drugs before delivery, withdrawal symptoms (convulsions, breathing problems, vomiting, diarrhea, eating disorders, etc.) may occur in newborns after

delivery. (3) Administration during pregnancy may cause bleeding tendency in newborns. It may happen.

(4) It has been reported that administration during pregnancy causes a decrease in folic acid. There is.

(5) It should be administered to lactating women only if the therapeutic benefits are judged to outweigh the risks. [It has been reported that it passes into breast milk.]]

7. Overdose 3) Signs

and symptoms: The first signs and symptoms usually appear 1 to 3 hours after taking the drug. Central nervous system disorders (tremors, excitement, convulsions, disturbances of consciousness, coma, electroencephalogram changes, etc.) are the most obvious, and cardiovascular disorders (blood pressure changes, electrocardiogram changes, etc.) are usually mild. Additionally, rhabdomyolysis may occur.

Treatment: No specific antidote known. Typically, the following actions are taken: • Emesis, aspiration of gastric contents, gastric lavage, hemodialysis. Administer activated charcoal if necessary. • Secure the airway. Endotracheal intubation, artificial respiration, and oxygen inhalation as necessary. •For hypotension, raise both legs and administer plasma volume expanders. Administer vasopressors as necessary. - Inject diazepam intravenously for convulsions (however, be careful of respiratory depression, hypotension, and worsening of coma due to diazepam). After taking appropriate measures, continue to monitor breathing, cardiac function, blood pressure, body temperature, etc. for several days.

8. Precautions for

application : When delivering medicines: Instruct patients to take out PTP-packaged medicines from the PTP sheet before taking them. (It has been reported that if a PTP sheet is accidentally ingested, the hard, sharp edges may penetrate the esophageal mucosa, causing perforation and causing serious complications such as mediastinal sinusitis.)

9. Other precautions (1)

When switching to another antiepileptic drug, it is usually recommended to use diazepam or a barbiturate compound in combination to prevent exacerbation. (2) In an experiment in which carbamazepine was orally administered to rats over a long period of time (25, 75, and 250 mg/kg for 2 years), it was reported that the occurrence of liver tumors in females was significantly observed in a dose-dependent manner. be.

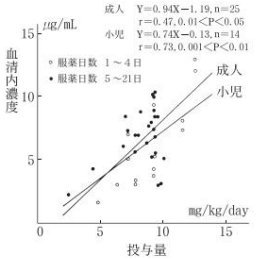
(3) Abnormalities in serum immunoglobulin (IgA, IgG, etc.) may appear. (4) There are reports of male fertility impairment and abnormal spermatogenesis. (5) There have been reports of cross-sensitivity (skin hypersensitivity including hypersensitivity syndrome) occurring between this drug and other antiepileptic drugs (phenytoin, phenobarbital). (6) In a retrospective genome-wide association analysis in Japanese subjects, HLA-A* 3101 was found among cases of severe drug eruptions such as oculomucocutaneous syndrome, toxic epidermal necrolysis, and hypersensitivity syndrome caused by this drug. It has been reported that 58% (45/77) were *carriers of HLA-A** 3101, and 13% (54/420) of the population who did not develop severe drug eruption were carriers of HLA-A*3101. 4) The frequency of HLA-A* 3101 allele is reported to be 0.071-0.120 in Japanese people. 5) In a study on patients of Han-Chinese ancestry, almost all of the cases of oculomucocutaneous syndrome and toxic epidermal necrolysis caused by this drug had HLA-B* 1502 . There are reports that he was a person. 6, 7) On the other hand, studies in Japanese subjects have not suggested a clear relationship between *cases of severe drug eruption caused by this drug and HLA-B** 1502 possession. 4) It has been reported *that the frequency of the HLA-B** 1502 allele is 0.019-0.124 in Han Chinese and 0.001 in Japanese. 5) (7) The results of 199 placebo-controlled clinical trials of multiple anti-epileptic drugs, including this drug, conducted overseas targeting epilepsy, mental disorders, etc., show that the occurrence of suicidal ideation and suicide attempts has been significantly reduced. The risk was approximately twice as high in the antiepileptic drug group compared to the placebo group (antiepileptic drug group: 0.43%, placebo group: 0.24%); This was calculated to be 1.9 more people per 1,000 people (95% confidence interval: 0.6-3.9). It was also calculated that in the subgroup of patients with epilepsy, there were 2.4 more patients per 1,000 compared to the placebo group.

ÿPharmacokineticsÿ

1. Blood concentration 8)

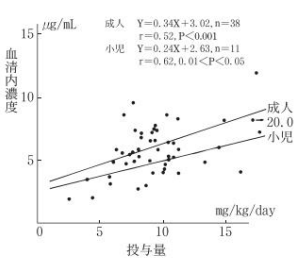
The relationship between the serum concentration and the dose in epilepsy patients receiving monotherapy with carbamazepine is shown in the figure below.Although there are large individual differences, in the early stages of treatment, a high serum concentration was obtained compared to the dose (Fig. 1), and then decreases (Figure 2). The serum concentration/dose ratio increases until the 10th day of administration, but then decreases, and the serum concentration fluctuates depending on the number of days of drug administration; this is due to self-induction of drug-metabolizing enzymes. It is believed that. Furthermore, when comparing children (6 to 13 years old) and adults (14 to 64 years old), it is thought that children show lower values because carbamazepine is metabolized faster in children.

Figure 1 (Drug administration days 1 to 21)



小児と成人を合算すると
回帰直線はY＝0.80X－0.11,
r＝0.60, p＜0.001となる。

Figure 2 (Number of days on medication: 22 to 7,833 days)



小児と成人を合算すると
回帰直線はY＝0.26X＋3.40,
r＝0.47, p＜0.01となる。

2. Absorption and excretion9-14)

Carbamazepine is absorbed relatively slowly from the gastrointestinal tract, and peak blood concentrations are achieved after 4 to 24 hours after a single dose. Carbamazepine is 70-80% bound to plasma proteins, and the concentration of unchanged carbamazepine in saliva closely reflects the non-protein bound carbamazepine (20-30%) in plasma. The half-life of the unchanged drug in the blood after a single administration is approximately 36 hours, but when administered repeatedly, it becomes 16 to 24 hours due to auto-induction of drug-metabolizing enzymes, and further induction of other enzymes may occur. When used in combination with antiepileptic drugs, the duration is reduced to 9 to 10 hours. The urinary excretion rate of the unchanged drug is only 2 to 3% of the administered dose, regardless of single or repeated administration, and is mainly excreted by pharmacologically active metabolites such as carbamazepine-10, 11-epoxide. excreted as (Foreigner data)

[Clinical results] Overall improvement in 309 cases in which efficacy was determined in clinical trials including mania, manic state in manic-depressive disorder, and **excited state in schizophrenia (additional efficacy)** double-blind comparative study The rate was 66.5% (103/155) for endogenous mania and 51.9% (80/154) for schizophrenia. The usefulness of this drug has been confirmed in a double-blind comparative study.

[Medicine efficacy pharmacology]

1. Anticonvulsant action 15)

Carbamazepine exhibits almost the same suppressive effect as phenobarbital on electric shock convulsions in rats, and has a sufficient suppressive effect on strychnine convulsions in mice injected intraperitoneally with 2.5 mg/kg of strychnine. Although it does not exhibit a suppressive effect, carbamazepine at a level of 100 mg/kg (oral) clearly prolongs the onset of convulsions compared to diphenylhydantoin and mephenesin. It does not show very strong protective effects against pentetrazole convulsions (mice) and picrotoxin convulsions (mice).

stomach.

2. Effect on kindling16) Carbamazepine and phenobarbital suppress the formation of kindling induced by stimulation of the amygdala nucleus in cats, showing a preventive effect against the acquisition of epileptogenicity, but phenytoin does not. In this case, phenobarbital suppresses the development of clinical symptoms rather than the development of afterfire, whereas carbamazepine has been shown to suppress the development of afterfire and the acquisition of secondary epileptogenicity. On the other hand, for complete kindling convulsions, carbamazepine, phenobarbital, and phenytoin all exhibit suppressive effects (anticonvulsant effects) at serum levels below toxic doses.

3. Effects on cerebral afterdischarge and evoked responses17, 18)

Later firings of the motor cortex, lentiform nucleus, and ventrolateral thalamic nucleus in cats are hardly inhibited by carbamazepine, or are only mildly and briefly inhibited. Furthermore, post-firing from the amygdala nucleus and hippocampus was significantly suppressed, indicating that carbamazepine acts selectively to the limbic system rather than the neocortical system.

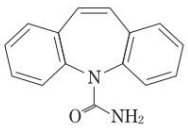
4. Antiexcitatory effect Behavioral pharmacologically, in tests using mice, carbamazepine has been shown to suppress combative behavior15, 19), inhibit stereotyped behavior20), and enhance anesthesia15). It is recognized that it has a calming effect. Electrophysiologically, tests using rabbits have shown that evoked potentials in the emotional pathway from the olfactory bulb to the limbic system (olfactory bulb-amygdaloid nucleus, olfactory bulb-hippocampus) are suppressed. twenty one)

5. Effect on trigeminal nerve evoked potential22)

In experiments using cats, administration of 10 mg/kg (intraperitoneal) of carbamazepine was observed to suppress evoked potentials recorded at the medullary level of the trigeminal nerve and the centromedial nucleus of the thalamus due to electrical stimulation of the facial skin.

[Physical and chemical knowledge regarding active ingredients]

Construction formula:



Generic name: Carbamazepine Chemical name: 5H-Dibenz[b, f]azepine-5-carboxamide Molecular formula: C15H12N2O Molecular weight: 236.27 Properties: White to slightly yellowish white powder, odorless and tasteless. But slightly bitter afterwards. Easily soluble in chloroform, slightly soluble in ethanol (95) or acetone, extremely soluble in water or diethyl ether. Melting point: 189 to 193ÿ Partition coefficient: 57.9 (1-octanol/pH7.4 phosphate buffer)

ÿÿ **[Packaging] Tegretol**

Tablets 100mg 100 tablets (PTP) 500 tablets (bulk)

Tegretol Tablets

200mg 100 tablets (PTP) 500 tablets (bulk)

Tegretol fine granules 50% 100g

ÿMain documentsÿ

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ÿÿ **[Document request first]**

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