LENDORMIN® 0.25 mg tablets

Boehringer Ingelheim

Composition
1 tablet contains 0.250 mg
2-bromo-4-(2-chlorophenyl)-9-methyl-6H-thieno[3,2-f]
= [1,2,4]triazolo[4,3-a][1,4]diazepine (= brotizolam)
Excipients
lactose monohydrate, maize starch undried, sodium starch glycolate, cellulose microcrystalline, magnesium stearate, purified water

Properties
Pharmacotherapeutic group: Benzodiazepine derivatives
ATC-Code: N05CD09
Brotizolam is a hetrazepine which binds specifically and with high affinity to benzodiazepine receptors in the central nervous system.
It reduces time to sleep, number of awakenings , and it increases duration of sleep.
At the recommended doses, changes in sleep architecture measured by electroencephalographic activity occurred: the mean duration and percentage of REM sleep were reduced during the first 6 hours of sleep.

Pharmacokinetics
Absorption:
Following peroral administration brotizolam is rapidly absorbed from the GI tract. After a single oral dose of 0.25 mg, an average maximum plasma concentration of 5.5 ± 0.7 ng/mL attained within 45 ± 12 min is observed. The absorption is carried out as an apparent first-order process with absorption half-lives averaging 14.9 ± 8.5 min. The absolute bioavailability following peroral administration is approximately 70 %.

Distribution:
Brotizolam is 89-95% bound to human plasma proteins, and has an apparent half-life of distribution ranging from 7 to 26 min. The areas under the plasma concentration time curves (AUC) show values between 31.0 ± 5.7 ng h/mL and 56.6 ± 21.3 ng h/mL. Brotizolam is well distributed into the human body with a mean apparent volume of distribution of approximately 0.66 L/kg. In animals, brotizolam crosses the placental barrier and is also excreted in the breast milk.

Metabolism:
Brotizolam is metabolized through oxidative reactions in the liver by CYP3A4, being the hydroxylation at different sites of the brotizolam molecule, i.e. methyl group and diazepine ring, the preferred metabolic pathway.
All hydroxylated metabolites are almost completely conjugated to glucuronic acid and/or sulphuric acid. The hydroxylated metabolites are less active than the parent compound, and they are not considered to contribute to the clinical effects.

Elimination:
Approximately two thirds of the orally applied brotizolam dose is excreted renally, the rest with the feces. Less than 1% of the dose occurs in urine as parent compound. The major metabolites of brotizolam α-hydroxybrotizolam and 6-hydroxybrotizolam can be detected in urine at concentrations of 27% and 7%, respectively.
Other highly polar metabolites with probably more than one hydroxy group as well as a less polar substance than brotizolam can also be detected in urine.

The mean elimination half-life from plasma of brotizolam is short and varies between 3 and 8 hours in healthy subjects.
Brotizolam has been classified as a short-acting benzodiazepine. The mean apparent oral clearance values of brotizolam obtained after an oral dose of 0.25mg range from 128.36 to 188.37 mL/min. Differences observed can be attributed to determination methods used, i.e. RIA, GLC. Daily intake of 0.25 mg doses did not lead to accumulation or any changes in the pharmacokinetics of brotizolam as compared to single dose administration.

Special populations
Elderly
Following oral administration of 0.25 mg, the mean time to peak plasma concentration in elderly patients (mean age 82 years) is slightly higher than that observed in younger subjects (mean age 23 years), i.e. 1.7 h vs. 1.1 h. The mean peak concentration in elderly patients after the same oral dose is approx 5.6 ng/mL and shows no difference with that calculated in studies with young healthy subjects. The oral elimination half-life is significantly longer than that observed in young volunteers (9.1 h vs. 5.0 h, P<0.02). The absolute bioavailability of brotizolam in elderly patients is approximately 66%. After continuous administration of a 0.25-mg brotizolam dose for three weeks neither accumulation nor faster elimination of the drug is observed. Brotizolam demonstrates linear pharmacokinetics up to a dose of 1.5 mg .

Renal impairment
Pharmacokinetics of brotizolam is basically unchanged in patients with various degrees of renal failure (creatinine clearance: < 15 ml/min, 15-45 mL/min and 45 - 80 mL/min). Mean elimination half-life from plasma was determined to be 8.15 hours, 6.90 hours and 7.61 hours in patients with mild, moderate and severe renal insufficiency, respectively.

Liver impairment
The absorption peak time and the peak concentration of brotizolam in patients with liver cirrhosis are similar to those observed in healthy subjects. The protein binding and the clearance of unbound brotizolam are lower than those observed in healthy subjects, whereas the mean value of elimination half-lives is 12.8 hours (9.4-25 h).

Alcohol
Concomitant alcohol consumption results in a significant decrease of brotizolam clearance (1.85 mL/min/kg vs. 2.19 mL/min/kg), an increase of peak plasma concentrations (5.3 ng/mL vs. 4.3 ng/mL) and a prolonged terminal elimination half-life (5.2 h vs. 4.4 h).

Indications
Insomnia requiring pharmacological intervention.

Dosage and Administration
Posology
Unless otherwise prescribed by the physician, the following dosages are recommended:
Adults: 0.25 mg
Elderly: 0.125 mg - 0.25 mg

Treatment should be started with the lowest recommended dose. The recommended dose of 0.25 mg should not be exceeded because of the increased risk of unacceptable CNS-adverse effects.

Special populations
A reduction in dosage should be considered in the following patients. Tablets can be divided into equal halves for this purpose (see section Special precautions):
- with impaired liver function (see sections Contraindications and Pharmacokinetics)
- elderly (see section Pharmacokinetics)
- with chronic respiratory insufficiency with hypercapnia due to the risk of respiratory depression, especially at night (see section Contraindications)

In cases of impaired renal function, the data available show that a dose adaptation is not necessary (see section Pharmacokinetics).

Method of administration
LENDORMIN should be taken on an empty stomach with a little liquid just before going to bed. Alternatively, the tablet may be dissolved under the tongue.
Patients must allow a 7 - 8 hour period after taking LENDORMIN to rest/sleep.

Duration of treatment
Treatment should be as short as possible. The duration of treatment varies from a few days to a maximum of two weeks. It is recommended that the dosage be gradually decreased and the tapering-off-process should be tailored to the individual (see section Special precautions).
In certain cases extension beyond the maximum treatment period may be necessary; if so, it should not take place without re-evaluation of the patient's status.

Contraindications
LENDORMIN is contraindicated in patients with myasthenia gravis, severe respiratory insufficiency, sleep apnoea syndrome and severe hepatic insufficiency.
LENDORMIN is contraindicated in patients with a known hypersensitivity to the active ingredient brotizolam, any of the excipients or to other benzodiazepines.
The available dosage forms are only suitable for adults and no investigations have been performed in children. Therefore, LENDORMIN is contraindicated in children.
In case of rare hereditary conditions that may be incompatible with an excipient of the product (see section "Special precautions") the use of the product is contraindicated.

Special Precautions
Psychiatric conditions
Treatment with Brotizolam alone is not recommended in patients with psychotic illness. It should not be used alone in patients suffering from depression or anxiety associated with depression, as suicidal behaviour may be precipitated in such patients. Pre-existing depression may be unmasked.
Paradoxical reactions are known to occur with benzodiazepines. They are more likely to occur in the elderly. Restlessness, agitation, irritability and vivid nightmares have been reported in rare cases with brotizolam also at therapeutic doses. Should this occur, use of the product should be discontinued.

Dependence
Physical and psychic dependence may develop. The risk of dependence increases with dose and duration of treatment; it is also greater in patients with a history of alcohol or drug abuse where brotizolam should not be used.
Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. These withdrawal symptoms are e.g. headache, muscle pain, extreme anxiety and tension, restlessness, confusion or irritability. In severe cases the following withdrawal symptoms may occur: derealization, depersonalisation, hyperacusis, numbness and tingling of extremities, hypersensitivity to light, noise or physical contact, hallucinations or epileptic seizures.

Use with alcohol
Sedation, fatigue and impaired concentration may be enhanced when brotizolam is used in combination with alcohol (see section Interactions).

Tolerability
Some loss of efficacy to the hypnotic effects of short acting benzodiazepines may develop after repeated use over a few weeks.

Rebound anxiety and effect
One of the first symptoms of the development of dependence is the occurrence of rebound phenomena, whereby the symptoms that led to treatment with a benzodiazepine recur in an enhanced form after withdrawal of the drug. It may be accompanied by other reactions including mood changes, anxiety and restlessness.
Since the risk of withdrawal/rebound phenomena is greater after abrupt discontinuation of treatment, it is recommended that the dosage be gradually decreased.
It is important that patients are informed of the possibility of rebound phenomena in order to reduce anxiety about such symptoms in case they occur when the drug is withdrawn. It is useful to inform therefore the patient that treatment will be of limited duration, and to explain precisely how the dosage will be progressively decreased.

Amnesia
Benzodiazepines may induce anterograde amnesia, which may occur at therapeutic doses, the risk increasing at higher doses. Amnestic effects may be associated with abnormal behaviour. The condition occurs most often several hours after ingesting the product and therefore, to reduce the risk, patients should be instructed to ensure that they have sufficient uninterrupted sleep.

For the elderly and patients with impaired liver function, a reduction in dosage should be considered. The same precaution applies for patients with chronic respiratory insufficiency with hypercapnia due to the risk of respiratory depression, especially at night.
This product contains 82.75 mg of lactose monohydrate per tablet, which corresponds to the maximum recommended daily dose.
Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia should not take this medicine.
Somnambulistic behaviors, e.g. sleeping-driving, making phone call as well as preparing and eating food while asleep may occur.
Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Therefore, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. In case of concomitant prescription, limit dosages and durations to the minimum required and strictly monitor patients for signs and symptoms of respiratory depression and sedation.

Interactions
When brotizolam is prescribed with other CNS depressants, potentiation of central nervous effects may occur. Such potential interactions must be considered with a variety of agents including anti-psychotics (neuroleptics), hypnotics, anxiolytics, sedatives, antidepressants, narcotic analgesics, antiepileptics, anaesthetics and sedative antihistamines.
In the case of narcotic analgesics, potentiation of euphoria may enhance psychic dependence.
The concomitant use of benzodiazepines and opioids may increase the risk of sedation, respiratory depression, coma and death (see section Special warnings and precautions)
When brotizolam is used in combination with alcohol, sedation, fatigue and impaired concentration may be enhanced (see subsection „Alcohol" under the section "Pharmacokinetics").
In vitro interaction investigations suggest a relevant contribution of CYP 3A4 in the hepatic metabolism of brotizolam. The potential for pharmacokinetic drug-drug interactions and resulting alterations of brotizolam activity should therefore be taken into account, if brotizolam is administered together with inducers (potential for lack of efficacy of brotizolam, e.g. rifampicin) or inhibitors of CYP 3A4 (potential of increase of toxicity of brotizolam, e.g. ketoconazole).

Fertility, Pregnancy and Lactation

Pregnancy and lactation
There are no data from the use of brotizolam in pregnant or breast feeding women.
In animal experiments, brotizolam was not teratogenic. Embrotoxic or embryolethal effects were observed at high, maternally toxic doses (see Toxicology Section).
There is evidence that brotizolam and its metabolites cross the placental barrier and are excreted in the milk of lactating animals.
The product's pharmacological characteristics may predispose to effects in the neonate such as hypothermia, hypotonia and moderate respiratory depression.
Moreover, infants born to mothers who took benzodiazepines chronically during the later stages of pregnancy may have developed physical dependence.
Therefore, LENDORMIN is not recommended during pregnancy and lactation.

Fertility
No clinical data on fertility are available for brotizolam. Preclinical studies performed with brotizolam showed no adverse effects on fertility (see Toxicology Section).

Effects on ability to drive and use machines
No studies on the effect on the ability to drive and use machines have been performed. However, patients should be advised that they may experience undesirable effects such as sedation, amnesia and impaired psychomotor skills during treatment. Psychomotor impairment may increase the risk of fall and road traffic accident. Concurrent use of alcohol and/or CNS-depressant drugs will potentiate this impairment. If sleep is of insufficient duration, the likelihood of impaired alertness is increased.
Therefore, caution should be recommended when driving a car or operating a machinery.
If patients experience any of these events, they should avoid potentially hazardous tasks such as driving or operating machinery.

Adverse Reactions
Most adverse reactions that have been observed so far, relate to the product's pharmacological action. These phenomena are predominantly at the start of therapy and usually disappear with continued administration. The risk of drug dependence (e.g. rebound effect, altered mood, anxiety and restlessness) increases with the duration of therapy with LENDORMIN, which should not exceed two weeks. In particular, the following adverse reactions may occur:

Psychiatric disorders
Nightmare, Depression, Mood altered, Anxiety, Confusional state, Restlessness, Drug dependence, Emotional disorder, Abnormal behaviour, Agitation, Libido disorder

Nervous system disorders
Somnolence, Headache, Dizziness, Sedation, Depressed level of consciousness, Ataxia, Anterograde amnesia, Dementia*, Mental impairment*, Psychomotor skills impaired*

Eye disorders
Diplopia

Gastrointestinal disorders
Gastrointestinal disorder, Dry mouth

Hepatobiliary disorders
Liver disorder, Jaundice

Skin and subcutaneous tissue disorders
Skin reaction

Musculoskeletal and connective tissue disorders
Muscular weakness

General disorders and administration site conditions
Drug withdrawal syndrome, Paradoxical drug reaction, Rebound effect, Irritability, Fatigue

Investigations
Liver function test abnormal

Injury, poisoning and procedural complications
Road traffic accident*, Fall*

*) Class effect of benzodiazepines

Overdosage
Symptoms
Overdosage usually causes a very deep sleep, which may reach coma, depending on the amount ingested. It is usually not life-threatening if the patient is treated and if no agents such as barbiturates and/or alcohol have been taken.
Therapy
Special attention should be paid to respiratory and cardiovascular functions in intensive care. Flumazenil may be useful as an antidote. Forced diuresis and haemodialysis are expected to be of limited value in situations of pure benzodiazepine poisoning.

Toxicology
Brotizolam has a very low acute toxicity: Oral LD_{50} values were > 10 g/kg in mice and rats, and > 2 g/kg in rabbits and dogs. Clinical signs included ataxia and sedation in all species.
In oral repeat-dose toxicity studies in rats (gavage or dietary admixture) for up to 13 weeks, the No Observed Adverse Effect Level (NOAEL) was 0.3mg/kg/day and higher. No deaths occurred. Besides sedation, rats given 100 mg/kg/day and higher became aggressive. Drug tolerance developed. At the completion of treatment period, rats administered 400 mg/kg/day and higher showed enlarged liver and elevated serum cholesterol. Withdrawal signs occurred after cessation of treatment. All treatment related findings were reversible.
In an 18 months dietary study in rats, the NOAEL was 10mg/kg/day.
In rats given 400 mg/kg/day (equivalent to approximately 12000 times the MRHD base on a mg/mg² basis), an increase in mortality due poor general condition as well as histopathologic findings of phospholipidosis in the lung, pyelonephritis in the kidney and a trophy of testes were noted.
Rhesus monkeys tolerated 1 mg/kg/day for up to 12 months (NOAEL). At medium dose levels (10 or 7mg/kg/day for 3 or 12 months), ataxia, reduced activity and somnolence were observed. Increased appetite resulted in increased body weight and secondary effects thereof. At high dose levels (100 or 50 mg/kg/day), hyperreflexive muscular spasms occurred. Withdrawal signs were observed after cessation of treatment. All findings were reversible (3-month study).
Brotizolam was neither embryotoxic nor teratogenic at oral doses up to 30 mg/kg/day (rat) and 9 mg/kg/day (rabbit). In the rat, embryotoxic effects were noted at maternally toxic doses of 250 mg/kg/day and higher (equivalent to approximately 8000 times the MRHD based on a mg/mg² basis). Fertility was not impaired at doses up to 10 mg/kg/day. The NOAEL in a study on peri- and postnatal development in rats was 0.05 mg/kg/day. At 2.5mg/kg/day (equivalent to 80 times the MRHD based on mg/m² basis) and higher, which caused sedation and lower body weight gain in the dams, viability of pups was reduced during the lactation period. Increased offspring mortality was observed at 10 mg/kg/day and higher.
Results of various mutagenicity studies (Ames assay, bone marrow micronucleus test in mice, cytogenic test in Chinese hamster bone marrow and dominant lethal test in mice) were negative.
Brotizolam did not show a tumorigenic potential in the carcinogenicity study in mice given brotizolam up to 200 mg/kg. In the study in rats the NOAEL was 10 mg/kg/day. At 200 mg/kg/day, hyperplastic and neoplastic changes were seen in thyroids, thymus and uterus, but were considered species-specific, stress related or incidental and, therefore, not relevant for the use of the drug in man.

Availability
Tablets of 0.250 mg, 2-1000's pack in aluminum blisters of paper boxes.

Storage conditions
Store below 25°!
Store in a safe place out of the reach of children!

Manufactured by
Delpharm Reims
10 rue Colonel Charbonneaux, 51100 Reims, France
for
Boehringer Ingelheim International GmbH
Ingelheim am Rhein, Germany

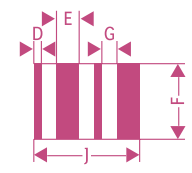
TFDA request+0095-06

319635-006

File information						Mandatory in	
						TD	Printfile
Issue date of TD:	07.08.2018					Yes	Yes
PPM SKU:	P009477					No	Yes
PPM SKU version:	006					No	Yes
Issue date of artwork:	08/Oct/2018					No	Yes
Print colors:	Pan Black	■	Pan 485	■			
Mat. No. Pack. Site:	319635-006					No	Yes
Min. font size :	7 pt						
Legend case version:	V4.0 01/OCT/2012 (please do not change or remove it)						
p2e:	920415 / 89029						

Technical information			
a = Batch No.		b = Expiry date	
c = Manufacturing date		d = Price/Sample/Clinic	
Technical colors			
BI-Diecut-Legendcase	■	Free area	Gluepoints

ADDITIONAL REQUIREMENT OF PACKAGING LINE
PPM SKU Description : PI LENDORMIN 0,25MG 100TABS TW
Dimension : 160 x 580 mm (FOLD. 160 x 290 mm)
No. of code : 88
Ref. drawing : PR34



MASS D 0,5 mm
MASS E 1,5 mm
MASS G 1,0 mm
MASS F 6,0 mm

Example
Technical information
control code

戀多眠® 錠0.25毫克（法國廠）
Lendormin® 0.25 mg Tablets

衛署藥輸字第025713號

成分
每錠含2-bromo-4-(2-chlorophenyl)-9-methyl-6H-thieno[3,2-f][1,2,4]-triazolo[4,3-a][1,4]diazepine (=brotizolam)　0.25毫克
賦形劑
lactose monohydrate, maize starch undried, sodium starch glycolate, cellulose microcrystalline, magnesium stearate, purified water

性質
藥物治療學分類：Benzodiazepine衍生物
ATC-Code：　N05CD09
Brotizolam爲一hetrazepine，對中樞神經系統之benzodiazepine接受體具特別的結合力及高親和力，可縮短入眠時間及減少覺醒次數，並增加睡眠時間。
在推薦劑量內，藉由腦電波活動測得其睡眠結構改變：REM睡眠的平均持續期間及比率在睡眠的前6個小時會降低。

藥物動力學
吸收：
Brotizolam口服後，可迅速地在胃腸道吸收。口服單劑0.25毫克之後，在45 ± 12分鐘之內可達到最高血中濃度(平均5.5 ± 0.7 ng/mL)。其吸收係以表觀一級速率指數反應方式(apparent first-order process)進行，吸收半衰期平均14.9 ± 8.5分鐘。本藥經口投予之絕對生體可用率約爲70%。

分佈：
Brotizolam 89%至95%會與人體的血漿蛋白結合，表觀分佈半衰期從7至26分鐘不等。血中濃度－時間曲線下面積(AUC)在31.0 ± 5.7 ngxh/mL至56.6 ± 21.3 ngxh/mL之間。Brotizolam可廣佈於人體，表觀分佈體積平均約爲0.66 L/kg。Brotizolam會通過動物的胎盤障蔽，也會從乳汁排出。

代謝：
Brotizolam在肝臟經由CYP3A4所催化的氧化反應進行代謝，brotizolam分子的不同位置(亦即，甲基及diazepine環)會被羥化(hydroxylation)，此爲主要的代謝途徑。

所有的羥化代謝產物皆爲幾乎完全與葡萄糖醛酸(glucuronic acid)及/或硫酸結合。羥化代謝產物的活性都低於原型化合物，一般認爲應不具臨床作用。

排除：
口服Brotizolam後，大約三分之二的劑量從腎臟排泄，其餘從糞便排出。低於1%的劑量在尿液中以原型存在。Brotizolam的主要代謝產物α-hydroxybrotizolam及6-hydroxybrotizolam可於尿液中偵測到分別爲27%及7%的濃度。
尿液中亦可偵測到其他可能具有一個以上羥基的高極性代謝產物以及一個極性低於brotizolam的物質。

Brotizolam在健康受試者的平均血漿排除半衰期相當短，從3至8小時不等。Brotizolam被歸類爲短效型benzodiazepine類藥物。口服0.25毫克之劑量後， brotizolam的平均表觀口服清除率從128.36至188.37 mL/min不等，此差異可歸因於所使用的檢測方法(亦即RIA、GLC)。與口服單一劑量相較，每天口服0.25毫克之總劑量並不會造成蓄積作用或導致brotizolam在藥物動力學上有任何變化。

特殊族群
年老病人
口服0.25毫克之劑量後，年老病人(平均年齡82歲)達到最高血中濃度的平均時間較年輕的受試者(平均年齡23歲)稍長，分別爲1.7小時與1.1小時。口服此劑量後，年老病人的最高血中平均濃度約爲5.6 ng/mL，與在針對年輕健康受試者的研究中所計算得到的數值並無差異。口服排除半衰期較在年輕健康受試者所觀察到者顯著較長(9.1相較於5.0小時，P<0.02)。Brotizolam在年老病人的絕對生體可用率約爲66%。在連續投予0.25毫克劑量之brotizolam三週之後，並不會造成藥物蓄積作用，藥物的排除也不會加速。Brotizolam的劑量增加至1.5毫克，其藥物動力學皆呈線性關係。

腎功能不全
對各種程度之腎衰竭病人(肌酸酐清除率[creatinine clearance]：<15mL/min、15-45mL/min、45-80mL/min)而言，brotizolam的藥物動力學未有改變。在輕度、中度或嚴重腎功能不全者，血漿之平均排除半衰期分別爲8.15小時、6.90小時、7.61小時。

肝功能不全
Brotizolam在肝硬化病人的吸收高峰時間及最高濃度皆與在健康受試者所觀察者相近。在此群病人，brotizolam與蛋白質的結合率以及未結合型brotizolam的清除率皆低於健康受試者，其排除半衰期的平均值爲12.8小時(9.4-25小時)。

酒精
併用酒精會顯著降低brotizolam之清除率(併用時爲1.85 mL/min/kg，未併用爲2.19 mL/min/kg)，增加最高血漿濃度(併用時爲5.3 ng/mL，未併用爲4.3 ng/mL)，及延長最終排除半衰期(併用時爲5.2小時，未併用爲4.4小時)。

適應症
失眠症的治療

用法用量
本藥須由醫師處方使用。
劑量
除非醫師另有處方，否則請依循下列建議劑量：
成人：　0.25毫克
年老者：　0.125毫克至0.25毫克
開始治療應使用最低建議劑量。劑量勿超過建議劑量0.25毫克，因爲超過此劑量會增加不被接受的中樞神經不良反應。

特殊族群
對於下列病人應考慮減低劑量，可將錠劑平分爲兩半後使用(請參閱「特別注意」一節):
- 肝功能不全(請參閱「禁忌症」及「藥物動力學」)
- 老年病人(請參閱「藥物動力學」一節)
- 慢性呼吸功能不健全併有高碳酸血症者，因爲呼吸抑制(尤以夜間爲著)的風險(請參閱「禁忌症」一節)

但腎功能不健全者，數據顯示無須調整劑量(請參閱「藥物動力學」一節)。

使用方法
戀多眠錠應於睡前空腹時與少量液體一起服用，也可經由舌下溶解吸收。
服用戀多眠錠後須確保病人有7–8小時的期間以供休息/睡眠。

治療期間
治療儘可能的短，治療時間可從幾天至最大期限兩個星期。建議應緩慢降低劑量且應依個人最適情況以達停藥(請參閱「特別注意」一節)。
某些病人在超過最大治療期時需要再延長治療時間，但需先再評估病人的狀況。

禁忌症
戀多眠錠禁用於重症肌無力，嚴重呼吸功能不健全，睡眠呼吸中止症候群，嚴重肝功能不全者。
戀多眠錠禁用於對本藥之主成分brotizolam、本藥之賦形劑、或對其他benzodiazepine類藥物過敏者。
目前現有的劑型僅適用於成人，且尚未有兒童的研究，所以戀多眠錠禁用於兒童。

本藥不可用於具有不適合使用本藥賦形劑之罕見遺傳狀況的病人(請參閱「特別注意」一節)。

特別注意
精神狀態
精神疾病病人並不應單獨使用brotizolam。不應單獨使用brotizolam於罹患抑鬱症或伴隨焦慮之抑鬱症病人，因爲這類病人可能發生自殺行爲。對原先就有抑鬱症者可能再現徵狀。

已知服用benzodiazepine類藥物曾發生非常規性反應，且較可能發生在年老者。曾有報告顯示極少數的病人在服用治療劑量的brotizolam時發生不安、焦躁、易怒及逼眞的惡夢。如發生這些症狀，應停藥。

依賴性
它可能造成身體及精神上的依賴。增加劑量及治療時間亦會增加賴藥的危險性；曾酗酒或吸毒者之賴藥危險性更嚴重，所以brotizolam不應使用於此類病人。

一旦已發生身體上的依賴，突然停藥將伴隨禁斷症狀。這些禁斷症狀如頭痛、肌痛、極端焦慮、緊張、不安、精神混亂或暴躁。嚴重者可能發生下列禁斷症狀：失去眞實感，喪失人格，聽覺過敏，四肢麻木及刺痛，對光、噪音或身體接觸過敏，幻覺或癲癇。

與酒精併用
Brotizolam與酒精併用時，鎮靜作用、疲勞及注意力減低的狀況可能加劇(請參閱「藥物交互作用」一節)。

耐受性
短效型之benzodiazepine重覆使用超過幾個星期後，某些病人可能會失去部分的安眠效能。

反彈性焦慮和效應
首先發生的依賴性症狀之一爲反彈現象，這現象將造成停藥後必須使用更強的benzodiazepine來治療，並可能併發其他反應如心情改變，焦慮及不安。
突然停藥會增加禁斷/反彈現象的危險性，所以推薦採用劑量漸減的方式停藥。
重要的是須告知病人可能發生停藥後的反彈現象以減少病人在實際反彈症狀發生時的焦慮。最好在治療開始時便告知病人此治療將進行一段期間，並解釋將會如何逐漸減低劑量。

健忘
Benzodiazepines可能會引起近事健忘 (anterograde amnesia)，此狀況可能發生於服用治療劑量時，劑量增加時此風險也會增加。健忘的效應可能伴隨異常的行爲。此狀況最常發生在服藥後數小時內，爲降低其危險性，需指示病人應確保有充足且不被干擾的睡眠。

年老及肝功能受損者應考慮減低劑量。慢性呼吸功能不全及高二氧化碳血症也須減低劑量，因其有呼吸抑制的危險性，尤其在夜間。

本藥物每錠含有82.75毫克的乳糖，相當於每日最高建議劑量中含有82.75毫克的乳糖。

具有半乳糖不耐症(例如半乳糖血症)之罕見遺傳狀況的病人不應使用本藥。
服用本品可能出現夢遊行爲，例如開車、打電話、以及準備與食用食物。
Benzodiazepine類藥品與opioid類藥品併用，可能導致重度鎮靜(profound sedation)、呼吸抑制、昏迷及死亡風險，故僅限於其他治療方式均無法達到預期效果時，方可考慮併用，且應使用最低有效劑量及最短治療時間，並嚴密監測病人是否有呼吸抑制及鎮靜等相關症狀。

藥物交互作用
Brotizolam與其他中樞神經抑制劑併服，有可能會加強中樞神經作用。本藥與抗精神病劑，安眠藥，抗焦慮劑，鎮靜劑，抗抑鬱劑，成癮性鎮痛劑，抗癲癇劑，麻醉藥及鎮靜性抗組織胺可能發生交互作用，併用時應列入考慮。
本藥與成癮性鎮痛劑併用時，其欣快感之增加可能會增強心理的依賴性。
同時使用Benzodiazepine藥物和opioid藥物可能會增加鎮靜、呼吸抑制、昏迷和死亡的風險(參見特別注意)。
Brotizolam與酒精併用時，鎮靜作用、疲勞、及注意力減低的狀況可能加劇(請參閱「藥物動力學」一節的「酒精」)。

活體外之交互研究顯示CYP3A4與brotizolam在肝臟的代謝有關。所以，如brotizolam與CYP3A4之誘發劑 (可能導致brotizolam缺乏療效，例如: rifampicin)或CYP3A4之抑制劑(可能增加brotizolam毒性，例如: ketoconazole)併用時，應考慮此可能造成藥物動力學上的藥物交互作用而導致brotizolam活性的改變。

生育力、懷孕與哺乳
懷孕與哺乳
尚無在孕婦及授乳婦使用brotizolam的資料。
Brotizolam在動物實驗中不具致畸胎性。在具母體毒性的高劑量下，可觀察到胚胎毒性及胚胎致死作用(請參閱「毒理學」一節)。
有證據顯示brotizolam及其代謝產物可通過胎盤障壁，也會從授乳動物乳汁排出。
本藥之藥理學特性可能造成新生兒體溫過低、張力過弱及呼吸輕微受抑制。
此外，母親於懷孕末期習慣性地服用benzodiazepin，嬰兒出生後可能已對此藥產生身體上的依賴。
所以孕婦及授乳婦不建議使用戀多眠錠。
生育力
尚無brotizolam對生育力之影響的臨床資料。臨床前研究顯示brotizolam對生育力無不良作用(請參閱「毒理學」一節)。

對駕駛及使用機械之能力的影響
尚未針對本藥對駕駛及使用機械能力的影響進行研究。不過，應告知病人，治療期間可能出現鎮靜作用、健忘、及知動能力(psychomotor skills)受損的不良作用。知動能力受損會增加摔跤及交通事故的風險。併用酒精及/或中樞神經抑制劑會加重前述不良影響。若睡眠時間不夠充足，警覺性變差的可能性會增加。因此，開車或操作機器時應謹慎。如病人出現任何這些狀況，即應避免開車或操作機器等可能具危險性的工作。

不良反應
目前有關本藥藥理學上大部份的不良反應已被觀察到。這些現象主要在治療開始時顯現，但繼續服藥後通常會消失。藥物依賴(例如回彈效應、情緒改變、焦慮、及不安)的風險會隨戀多眠錠治療時間增長而增加，因此治療時間不可超過兩週。下列爲特別可能發生的不良反應：

精神病症
惡夢、抑鬱症、情緒改變、焦慮、精神混亂、不安、賴藥性、情緒障礙、行爲異常、焦躁、性慾異常。

神經系統病症
睏倦、頭痛、眩暈、鎮靜作用、知覺減低、運動失調、近事健忘、失智*、心智障礙*、知動能力受損*

眼睛病症
複視

腸胃病症
腸胃病症、口乾

肝膽病症
肝臟病症、黃疸

皮膚及皮下組織病症
皮膚反應

肌肉骨骼及結締組織病症
肌肉無力

全身性病症及注射部位狀況
藥物禁斷症候群、非常規的藥物反應、回彈效應、暴躁、疲勞

檢驗
肝功能檢測結果異常

受傷、中毒、及程序併發症
交通事故*、摔跤*

*) benzodiazepine類藥物的同類效應。

過量
症狀
過量時，其症狀依劑量而異，通常發生極深度沈睡，甚至可能昏迷。
只要給予治療及病人未併服如barbiturates及/或酒之製劑，通常不會有生命危險。
治療
需加強照顧病人之呼吸及心血管功能。
Flumazenil爲一有用的解毒劑。
加強利尿作用及體透析對單純之benzodiazepine中毒的治療價值有限。

毒物學
急性毒性的研究顯示brotizolam的急性毒性極低：在小鼠及大鼠口服的LD_{50}都大於10g/kg，在兔子與狗也都大於2g/kg。在所有的動物皆出現運動失調及鎮靜的臨床徵象。

在一個以大鼠(強飼或添加於飼料)進行的口服重覆劑量達13週的毒性研究中顯示：大鼠的"無觀察到不良反應的劑量(NOAEL)"爲0.3mg/kg/天或更高，未發生死亡。而劑量達100mg/kg/天或更高劑量的大鼠除了鎮靜反應，亦變得躁動。產生耐藥性。治療結束時，劑量達400mg/kg/天或更高劑量之大鼠顯示其肝臟變大及血中膽固醇增加。停藥後發生禁斷現象。所有與治療相關的發現爲可逆性。
在一項18個月的飲食研究中，大鼠的NOAEL爲10mg/kg/天。

給予大鼠400mg/kg/天的劑量(以mg/m²計算，約相當於最大建議人類劑量[MRHD]的12000倍)時，因大鼠的整體健康狀況不佳而導致死亡率增加，並有肺磷脂症、腎盂腎炎、與睪丸萎縮等組織病理學檢查發現。

恆河猴對1mg/kg/天的劑量可耐受達12個月(NOAEL)。給予中等劑量(以10或7mg/kg/天治療3或12個月)時，曾觀察到出現運動失調、活動力減低、及睏倦。食慾增加導致體重增加及後續影響。給予高劑量(100或50 mg/kg/天)時會發生反射過強的肌肉痙攣。停藥後有禁斷現象。所有的發現皆具可逆性(爲期3個月的研究)。

Brotizolam在口服劑量達30mg/kg/天的大鼠及9 mg/kg/天的兔子並未發生胚胎毒性及致畸胎性。對大鼠的胚胎毒性是在具有母體毒性的250 mg/kg/天(以mg/m²計算，約相當於MRHD的8000倍)劑量或更高劑量時觀察到的。在劑量達10mg/kg/天也未發現生育力受損。出生前後及出生後發育的研究中，大鼠的"無觀察到不良反應發生，NOAEL"之劑量爲0.05mg/kg/天。給予母鼠可引發鎮靜作用及體重增幅降低的劑量2.5mg/kg/天(以mg/m²計算，相當於MRHD的80倍)或更高劑量時，觀察到授乳期間的幼鼠生存率減低。給予10 mg/kg/天或更高劑量時，幼獸死亡率增加。

多項致突變性的研究(Ames試驗、小鼠骨髓微核[micronucleus]試驗、中國倉鼠骨髓之細胞遺傳學試驗[cytogenic test]、與小鼠顯性致死試驗[dominant lethal tests])的結果皆爲陰性。

Brotizolam致癌性研究中顯示小鼠劑量達200mg/kg，也不會有發生惡性腫瘤的潛在性。在大鼠的研究中，無不良反應之劑量爲10mg/kg/天。在劑量達200mg/kg/天曾觀察到甲狀腺、胸腺及子宮發生增生及贅瘤的變化，此等現象被認爲具有物種專一性、與壓力有關、或爲偶發事件，因此與人類使用本藥無關。

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