

ATARAX®
Tablet

DRUG DESCRIPTION
ATARAX 0.25

Convex tablet with white color diameter 6 mm, upper initial mf and lower initial crossline.
The crossline is intended solely to facilitate ease of swallowing the medication, not for dose splitting.

ATARAX 0.5

Convex tablet with pink color diameter 6 mm, upper initial mf and lower initial crossline.
The tablet can be divided into two equal parts.

ATARAX 1

Convex tablet with violet color diameter 6 mm, upper initial mf and lower initial crossline.
The tablet can be divided into two equal parts.

COMPOSITIONS

Each tablet ATARAX 0.25 contains Alprazolam 0.25 mg
Each tablet ATARAX 0.5 contains Alprazolam 0.5 mg
Each tablet ATARAX 1 contains Alprazolam 1 mg

EXCIPIENTS

ATARAX 0.25

Lactose monohydrate, Corn starch, Povidone K30, Purified water, Sodium starch glycolate, Talc, Magnesium Stearate, Microcrystalline cellulose, Colloidal silicon dioxide.

ATARAX 0.5

Lactose monohydrate, Corn starch, Povidone K30, Purified water, Sodium starch glycolate, Talc, Magnesium Stearate, Microcrystalline cellulose, Colloidal silicon dioxide, Carnosine CI 14720.

ATARAX 1

Lactose monohydrate, Corn starch, Povidone K30, Purified water, Sodium starch glycolate, Talc, Magnesium Stearate, Microcrystalline cellulose, Colloidal silicon dioxide, Carnosine CI 14720, Indigotine CI 73015.

INDICATIONS

ATARAX Tablets are indicated for the treatment of:

1. Anxiety - including anxiety neurosis, anxiety disorders, symptoms of anxiety, etc.
2. Mixed Anxiety - Depression - including anxiety associated with depression.
3. Panic Disorders - including panic disorder with or without agoraphobia. The essential feature of panic disorder is the unexpected panic attack, a sudden onset of intense apprehension, fear, or terror.

PHARMACOLOGY AND METHOD OF ADMINISTRATION

Pharmacology

The optimum dosage of ATARAX Tablets should be individualized based upon the severity of the symptoms and individual patient response. The daily dosage (see Table) will meet the needs of most patients. In the few patients who require higher doses, dosage should be increased cautiously to avoid adverse effects. When higher dosage is required, the evening dose should be increased before the daytime doses. In general, patients who have not previously received psychotropic medications will require lower doses than those previously treated with minor tranquilizers, antidepressants, or hypnotics or those with a history of chronic alcoholism. Patients should be periodically reassessed and dosage adjustments made, as appropriate.

ATARAX Tablets	Usual Starting Dose	Usual Dose Range
Anxiety	0.75 to 1.5 mg daily, given in divided doses	0.5 to 4.0 mg daily, given in divided doses
Panic Disorders	0.5-1.0 mg given at bed-time or 0.5 mg three times daily	The dose should be adjusted to response. Dosage adjustments should be in increments no greater than 1 mg every three to four days. With ATARAX Tablets, additional doses can be added until a three times daily or four times daily schedule is achieved. The mean dose in a large multi-clinic study was 5.7 + 2.27 mg with occasional patients requiring a maximum of 10 mg daily.
Geriatric Patients	0.5 to 0.75 mg daily, given in divided doses	0.5 to 0.75 mg daily, given in divided doses; to be gradually increased if needed and tolerated.

The risk of dependence may increase with dose and duration of treatment, therefore, the lowest possible effective dose and duration should be used and the need for continued treatment reassessed frequently.
Discontinuation Therapy
The dosage should be reduced slowly in keeping with good medical practice. It is suggested that the daily dosage of ATARAX Tablets be decreased by no more than 0.5 mg every three days. Some patients may require an even slower dosage reduction.
Method of administration
The drug is given orally.

CONTRAINDICATIONS

ATARAX Tablets are contraindicated in patients with known hypersensitivity to benzodiazepines, alprazolam, or to any component of these products' formulation. ATARAX may be used in patients with open angle glaucoma who are receiving appropriate therapy, but is contraindicated in patients with acute narrow angle glaucoma.

SIDE EFFECTS

Side effects, if they occur, are generally observed at the beginning of therapy and usually disappear upon continued medication or decreased dosage.
Undesirable effects associated with alprazolam therapy in patients participating in controlled clinical studies and with post-marketing experience "Clinical studies conducted using the innovator product Xanax" are as follows:

Adverse Reactions Table					
System Organ Class	Very Common (≥ 1%)	Common (≥ 1/100 <1%)	Uncommon (≥ 1/1,000 <1/100)	Rare (≥ 1/10,000 <1/1,000)	Very Rare (≥ 1/100,000 <1/10,000)
Endocrine Disorders	-	-	-	-	-
Metabolic and Nutrition Disorders	-	Decreased appetite	-	-	-
Psychiatric Disorders	-	Confusional state, disorientation, libido decreased, anxiety, insomnia, nervousness, libido increased	Mania* (see section WARNINGS), hallucination*, anger*, agitation*, drug dependence	-	-
Nervous System Disorders	Sedation, somnolence, ataxia, memory impairment, dizziness, headache	Balance disorder, coordination abnormal, disturbance in attention, hypersomnia, scharg, tremor	Amnesia	-	-
Eye Disorders	Conjunctivitis, dry mouth	Nausea	-	-	-
Gastrointestinal Disorders	-	-	-	-	-
Hepatology Disorders	-	-	-	-	-
Skin and Subcutaneous Tissue Disorders	-	-	-	-	-
Musculoskeletal Disorders	-	-	-	-	-
Connective Tissue and Bone Disorders	-	-	-	-	-
Respiratory and Urinary Disorders	-	-	-	-	-
Reproductive System and Breast Disorders	-	-	-	-	-
General Disorders and Administration Site Conditions	-	-	-	-	-
Investigations	-	-	-	-	-

*ADR identified post-marketing

In many of the spontaneous case reports of adverse behavioral effects, patients were receiving other CNS drugs concomitantly and/or were described as having underlying psychiatric conditions. Patients who have borderline personality disorder, a prior history of violent or aggressive behavior, or alcohol or substance abuse may be at risk for such events. Instances of irritability, hostility and intrusive thoughts have been reported during discontinuance of alprazolam in patients with post-traumatic stress disorder.
In addition, the following adverse events have been reported in association with the use of anxiolytic benzodiazepines including alprazolam, anorexia, fatigue, and slurred speech.
The most common adverse reactions in patients with panic-related disorders were drowsiness, and slurred speech. Less common adverse reactions were altered mood and intellectual impairment/confusion.

WARNINGS AND PRECAUTIONS

Warnings

Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Limit dosages and durations to the minimum required.
Usage has not been established in depression with psychosis features, in bipolar disorders or in "endogenous" depression (i.e., severely depressed in-patients).
Habituation and emotional/physical dependence may occur with benzodiazepines, including alprazolam. As with all benzodiazepines, the risk of dependence increases with higher doses and long-term use and is further increased in patients with a history of alcoholism or drug abuse. Drug abuse is a known risk for alprazolam and other benzodiazepines, and patients should be monitored accordingly when receiving alprazolam. Alprazolam may be subject to diversion. There have been reports of overdose-related deaths when alprazolam is abused with other central nervous system (CNS) depressants including opioids, other benzodiazepines, and alcohol. These risks should be considered when prescribing or dispensing alprazolam. To reduce these risks the smallest appropriate quantity should be used and patients should be advised on the proper storage and disposal of unused drug.
ATARAX Tablets are not recommended for use in patients whose primary diagnosis is schizophrenia. Episodes of hypomania and mania have been reported in association with the use of alprazolam in patients with depression.

Precautions

As with other CNS active drugs, patients receiving ATARAX Tablets should be advised not to operate motor vehicles or dangerous machinery until it is established that they do not become drowsy or dizzy while receiving medication.
Withdrawal symptoms have occurred following rapid decrease or abrupt discontinuance of benzodiazepines including alprazolam. Therefore, dosage must be gradually tapered to preclude sequelae of rapid withdrawal. These can range from mild dysphoria and insomnia to a major syndrome which may include abdominal and muscle cramps, vomiting, sweating, tremor and convulsions. These signs and symptoms, especially the more serious ones, are generally more common in those patients who have received excessive doses over an extended period of time. However, withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken at therapeutic levels. Consequently, abrupt discontinuation should be avoided and a gradual tapering in dosage followed. When therapy is discontinued in patients with panic-related disorders, the symptoms associated with recurrence of panic attacks often mimic those of withdrawal.
Administration to severely depressed or suicidal patients should be done with appropriate precautions and appropriate size of pretest doses. Panic-related disorders have been associated with primary and secondary major depressive disorders and increased reports of suicide among untreated patients. Therefore, the same precaution must be exercised when using the higher doses of ATARAX Tablets in treating patients with panic-related disorders as is exercised with the use of any psychotropic drug in treating depressed patients or those in whom there is reason to expect concealed suicidal ideation or plan.
It is recommended that the dosage be limited to the smallest effective dose to preclude the development of ataxia or oversedation which may be a particular problem in elderly or debilitated patients. The usual precautions for treatment of renal or hepatic function should be observed.
The safety and efficacy of ATARAX Tablets in children less than 18 years of age have not been established.

DRUG INTERACTIONS

Benzodiazepines, including alprazolam, produce additive CNS depressant effects, including respiratory depression, when co-administered with opioids, other psychotropic medications, anticonvulsants, antihistaminics, ethanol and other drugs which themselves produce CNS depression.
The steady state plasma concentrations of imipramine and desipramine have been reported to be increased an average of 31% and 20%, respectively, by the concomitant administration of ATARAX Tablets in doses up to 4 mg/day. The clinical significance of these changes is unknown.
Pharmacokinetic interaction of alprazolam is administered along with drugs that interfere with its metabolism. Compounds which inhibit certain hepatic enzymes (particularly cytochrome P4503A4) may increase the concentration of alprazolam and enhance its activity. Data from clinical studies with alprazolam, in vitro studies with alprazolam, and clinical studies with drugs metabolized similarly to alprazolam provide evidence for varying degrees of interaction and possible interaction with alprazolam for a number of drugs "Clinical studies conducted using the innovator product Xanax". Based on the degree of interaction and the type of data available, the following recommendations are made:

- The co-administration of alprazolam with ketoconazole, itraconazole, or other azole type antifungals is not recommended.
- Caution and consideration of dose reduction is recommended when alprazolam is co-administered with nefazodone, fluvoxamine and cimetidine.
- Caution is recommended when alprazolam is co-administered with fluoxetine, propoxyphene, oral contraceptives, diazepam, or macrolide antibiotics such as erythromycin and troleandomycin.
- Interactions involving human immunodeficiency virus (HIV) protease inhibitors (e.g., ritonavir) and alprazolam are complex and time dependent. Low doses of ritonavir resulted in a large impairment of alprazolam clearance, prolonged its elimination half-life and enhanced clinical effects. However, upon extended exposure to ritonavir, CYP3A4 induction offset this inhibition. This interaction will require a dose-adjustment of alprazolam.
- Increased digoxin concentrations have been reported when alprazolam was given, especially in elderly (>65 years of age). Patients who receive alprazolam and digoxin should therefore be monitored for signs and symptoms related to digoxin toxicity.

Carcinogenesis

No evidence of carcinogenic potential was observed during 2-year bioassay studies of alprazolam in rats at doses up to 30 mg/kg/day (150 times the maximum recommended daily human dose of 10 mg/day) and in mice at doses up to 10 mg/kg/day (50 times the maximum recommended daily human dose of 10 mg/day).

Mutagenesis

Alprazolam was not mutagenic in the *in vitro* Ames test. Alprazolam did not produce chromosomal aberrations in the *in vivo* micronucleus assay in rats up to the highest dose tested of 100 mg/kg, which is 500 times greater than the maximum recommended daily human dose of 10 mg/day. Alprazolam also was not mutagenic *in vitro* in the DNA Damage/Alkaline Elution.

Fertility

Alprazolam produced no impairment of fertility in rats up to the highest dose tested of 5 mg/kg/day, which is 25 times the maximum recommended daily human dose of 10 mg/day.

Ocular Effects

When rats were treated orally with alprazolam at 3, 10, and 30 mg/kg/day (15 to 150 times the maximum recommended daily human dose of 10 mg/day) for 2 years, a tendency for a dose related increase in the number of cataracts (females) and corneal vascularization (males) was observed. These lesions did not appear until after 11 months of treatment.

Effect of Anesthetic and Sedative Drugs

Nonclinical research has shown that administration of anesthetic and sedation drugs that block N-methyl-D-aspartate (NMDA) receptors and/or potentiate gamma-aminobutyric acid (GABA) activity can increase neuronal cell death in the brain and result in long term deficits in cognition and behavior of juvenile animals when administered during the period of peak brain development. Based on comparisons across nonclinical species, the window of vulnerability of the brain to these effects is believed to correlate with human exposures in the third trimester of pregnancy through the first year of life, but may extend to approximately 3 years of age. While there is limited information of this effect with alprazolam, since the mechanism of action includes potentiation of GABA activity, a similar effect may occur. The relevance of these nonclinical findings to human use is unknown.

Pregnancy

An increased risk congenital malformations associated with minor tranquilizers (chloridazepoxide, diazepam and meprobamate) during the first trimester of pregnancy has been suggested in several studies. Because the use of these drugs is rarely a matter of urgency, the use of ATARAX Tablets during this period should almost always be avoided. The possibility that a woman of childbearing potential may be pregnant at the time of institution of therapy should be considered. Patients should be advised that if they become pregnant they should communicate with their physician about the desirability of discontinuing the drug.

Nursing Mothers

Levels of benzodiazepines, including alprazolam, in breast milk are low. However, nursing should not be undertaken while using benzodiazepines.

OVERDOSAGE

Symptoms of overdose with alprazolam are extensions of its pharmacological action. Manifestation of alprazolam overdosage include somnolence, confusion, impaired coordination, slurred speech, respiratory depression, diminished reflexes and coma. Death has been reported in association with overdoses of alprazolam by itself, as it has with other benzodiazepines. In addition, fatalities have been reported in patients who have overdosed with a single benzodiazepine, including alprazolam, and alcohol. Alcohol levels seen in some of these patients have been lower than those usually associated with alcohol-induced fatality.

Experiments in animals have indicated that cardiopulmonary collapse can occur following massive intravenous doses of alprazolam (over 195 mg/kg; 975 times the maximum recommended daily human dose of 10 mg/day). Animals could be resuscitated with positive mechanical ventilation and the intravenous infusion of norepinephrine bitartrate.
Treatment of overdosage is primarily supportive of respiratory and cardiovascular function. The value of dialysis has not been determined. Flumazenil may be used as an adjunct to the management of respiratory and cardiovascular function associated with overdosage.

STORAGE

Store at temperature below 30°C, protect from light.
Keep out of the reach of children.

PRESENTATION AND REGISTRATION NUMBER

Box, 10 blisters @ 10 tablets of ATARAX 0.25, Reg. No. DPL2133313210C1
Box, 10 blisters @ 10 tablets of ATARAX 0.5, Reg. No. DPL0133313210B1
Box, 10 strips @ 10 tablets of ATARAX 1, Reg. No. DPL1633313210A1

For reporting Side Effects and Product Complaints, please contact:
PT. Mersifarma Pharmacovigilance Team

Email : farmakovigilans@mersifarma.com
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ON MEDICAL PRESCRIPTION ONLY

Manufactured by:

PT. Mersifarma

PT. Mersifarma TM
Sukabumi - Indonesia
0000008-0000000-00

ATARAX®
Tablet

Pemeriksaan Obat

ATARAX 0.25

Tablet cembung warna putih, diameter 6 mm, penandaan atas mf dan penandaan bawah crossline.
Garis bagi hanya untuk memfasilitasi kemudahan pasien dalam menelan obat, tidak untuk pembagian dosis.

ATARAX 0.5

Tablet cembung warna merah muda, diameter 6 mm, penandaan atas mf dan penandaan bawah crossline.
Tablet dapat dibagi menjadi dua bagian yang sama besar.

ATARAX 1

Tablet cembung warna ungu muda, diameter 6 mm, penandaan atas mf dan penandaan bawah crossline.
Tablet dapat dibagi menjadi dua bagian yang sama besar.

KOMPOSISI

Tablet ATARAX 0.25 mengandung Alprazolam 0.25 mg
Tablet ATARAX 0.5 mengandung Alprazolam 0.5 mg
Tablet ATARAX 1 mengandung Alprazolam 1 mg

ZAT TAMBAHAN

ATARAX 0.25

Lactose monohydrate, Corn starch, Povidone K30, Purified water, Sodium starch glycolate, Talc, Magnesium Stearate, Microcrystalline cellulose, Colloidal silicon dioxide.

ATARAX 0.5

Lactose monohydrate, Corn starch, Povidone K30, Purified water, Sodium starch glycolate, Talc, Magnesium Stearate, Microcrystalline cellulose, Colloidal silicon dioxide, Carnosine CI 14720.

ATARAX 1

Lactose monohydrate, Corn starch, Povidone K30, Purified water, Sodium starch glycolate, Talc, Magnesium Stearate, Microcrystalline cellulose, Colloidal silicon dioxide, Carnosine CI 14720, Indigotine CI 73015.

INDIKASI

Tablet ATARAX diindikasikan untuk pengobatan:

1. Kecemasan – termasuk neurosis kecemasan, gangguan kecemasan, gejala kecemasan, dan sebagainya.
2. Kecemasan Campuran dengan Depresi – termasuk kecemasan yang berhubungan dengan depresi.
3. Gangguan Panik – termasuk gangguan panik dengan atau tanpa agoraphobia. Ciri utama dari gangguan panik adalah serangan panik tak terduga, yaitu munculnya rasa takut, cemas, atau terror yang intens secara tiba-tiba.

PHARMACOLOGY AND CARA PEMBERIAN

Pharmacology

Dosis optimal ATARAX Tablet harus disesuaikan secara individual berdasarkan tingkat keparahan gejala dan respons pasien masing-masing. Dosis harian (lihat Tabel) akan memenuhi kebutuhan sebagian besar pasien. Pada pasien yang memerlukan dosis lebih tinggi, dosis harus ditingkatkan dengan hati-hati untuk menghindari efek samping. Ketika dosis lebih tinggi diperlukan, dosis malam hari harus ditingkatkan terlebih dahulu sebelum dosis siang hari. Secara umum, pasien yang belum pernah menerima obat psikotropika sebelumnya akan memerlukan dosis lebih rendah dibandingkan mereka yang sebelumnya telah mendapat dengan penangan ringan, antidepressan, atau hipnotik, atau mereka dengan riwayat alkoholisme kronis. Pasien harus dievaluasi kembali secara berkala dan penyesuaian dosis dilakukan sesuai kebutuhan.

Tablet ATARAX	Dosis Awal yang Umum	Rentang Dosis yang Umum
Kecemasan	0.75 hingga 1.5 mg setiap hari, diberikan dalam dosis terbagi	0.5 hingga 4.0 mg setiap hari, diberikan dalam dosis terbagi
Gangguan Panik	0.5-1.0 mg diberikan pada waktu tidur atau 0.5 mg tiga kali sehari	Dosis harus disesuaikan dengan responsnya. Penyesuaian dosis harus dalam kenaikan tidak lebih dari 1 mg setiap tiga hingga empat hari. Dengan Tablet ATARAX, dosis tambahan bisa ditambahkan hingga tercapainya jadwal tiga kali sehari atau empat kali sehari. Dosis rata-rata dalam sebuah penelitian multiklinik berskala besar adalah 5.7 ± 2.27 mg dengan sesekali pasien memerlukan dosis harian hingga maksimum 10 mg.
Pasien Lanjut Usia	0.5 hingga 0.75 mg setiap hari, diberikan dalam dosis terbagi	0.5 hingga 0.75 mg setiap hari, diberikan dalam dosis terbagi; untuk ditingkatkan secara bertahap jika diperlukan atau dapat ditoleransi.

Risiko ketergantungan dapat meningkat seiring dengan dosis dan durasi pengobatan, oleh karena itu, dosis efektif terendah dan durasi pengobatan yang paling singkat harus digunakan dan kebutuhan untuk melanjutkan pengobatan harus dievaluasi kembali secara berkala.

Indikasi

Dosis harus dikurangi secara perlahan sesuai dengan praktik medis yang baik. Disarankan agar dosis harian ATARAX Tablet dikurangi tidak lebih dari 0,5 mg setiap tiga hari. Beberapa pasien mungkin memerlukan pengurangan dosis yang lebih lambat.

Cara pemberian

Obat diberikan secara oral.

KONTRAINDIKASI

Tablet ATARAX dikontraindikasikan pada pasien dengan hipersensitivitas yang diketahui terhadap benzodiazepin, alprazolam, atau terhadap komponen apa pun dari formulasi produk ini. ATARAX dapat digunakan pada pasien dengan glaukoma sudut terbuka yang menerima terapi yang sesuai, namun dikontraindikasikan pada pasien dengan glaukoma sudut sempit akut.

EFEK SAMPING

Efek samping, jika terjadi, umumnya teramat pada awal terapi dan biasanya menghilang setelah pengobatan dilanjutkan atau dosis dikurangi.
Efek yang tidak diinginkan terkait dengan terapi alprazolam pada pasien yang berpartisipasi dalam studi klinis terkontrol dan pengalaman pasca-pemasaran "Studi klinis yang dilakukan menggunakan produk inovator Xanax" adalah sebagai berikut:

Tabel Reaksi Merugikan					
Kelas Organ Sistem	Sangat Umum <1/100	Umum <1/100 hingga <1/10	Tidak Umum <1/100 hingga <1/1000	Sangat Jarang <1/10000	Frekuen Tidak Diketahui (tidak dapat ditentukan dari data yang tersedia)
Gangguan Endokrin	-	-	-	-	-
Gangguan Metabolisme dan Nutrisi	-	Penurunan nafsu makan	-	-	-
Gangguan Psikiatri	Depresi	Kondisi bingung, disorientasi, penurunan libido, kecemasan, insomnia, pengurangan libido, gangguan*	Mania* (lihat bagian 14, haluanas*) anoreksia, agitasi*, ketergantungan obat*	-	Hipomania* agresif*, sikap permusuhan*, berpikir abnormal*, hiperaktivitas, psikomotorik*, penyalahgunaan obat-obatan*
Gangguan Sistem Saraf	Sedasi, somnolensi, ataksia, gangguan memori, disartria, pusing, sakit kepala	Gangguan keseimbangan, koordinasi abnormal, gangguan perhalalan, hipersomnia, lemah, tremor	Amnesia	-	Ketidakseimbangan sistem saraf otonom*, distonia*
Gangguan Mata	-	Penglihatan kabur	-	-	-
Gangguan Gastrointestinal	Konstipasi, mulut kering	Mual	-	-	-
Gangguan Hepatobilier	-	-	-	-	-
Gangguan Jantung dan Subkutan	-	Dermatitis*	-	-	-
Gangguan Muskuloskeletal, Jantung, Bat, dan Tulang	-	-	-	-	-
Gangguan Ginjal dan Perikutan	-	-	-	-	-
Gangguan Sistem Reproduksi dan Payudara	-	Disfungsi seksual*	-	-	-
Gangguan Umum dan Kondisi di Lokasi Pemberian	-	Ket lelah, instabilitas	-	-	-
Pemeriksaan	-	Penurunan berat badan, kelemahan berat badan	-	-	-

*ADR yang diidentifikasi setelah pemasaran

Dalam banyak laporan kasus spontan mengenai efek samping perilaku yang merugikan, pasien yang melaporkan mengalami efek samping tersebut sedang menerima obat-obatan sistem saraf pusat (CNS) lainnya secara bersamaan dan/atau digambarkan memiliki kondisi psikiatri yang mendasarinya. Pasien yang memiliki gangguan kepribadian ambang, riwayat perilaku kekerasan, agresi sebelumnya, atau penyalahgunaan alkohol atau zat dapat berisiko mengalami kejadian-kejadian tersebut. Kejadian seperti itu, kejadian buruk berikutnya ini telah dilaporkan terkait dengan penggunaan benzodiazepin anxiolytic termasuk alprazolam, anoreksia, kelelahan, dan bicara cadet.
Efek samping yang paling umum pada pasien dengan gangguan terkait panik adalah kantuk dan bicara cadet. Efek samping yang kurang umum adalah perubahan suasana hati dan gangguan intelektual berupa kebingungan.

PERINGATAN DAN PERHATIAN

Peringatan

Penggunaan bersamaan benzodiazepin dan opioid dapat menyebabkan sedasi berat, depresi napas, koma, dan kematian. Dosis dan durasi terapi harus dibatasi seminimal mungkin sesuai kebutuhan. Penggunaan belum terbukti efektif pada kondisi depresi dengan fitur psikotik, gangguan bipolar, atau depresi endogen (yaitu pasien rawat inap dengan depresi berat).
Kebiasaan penggunaan (habituasi) dan ketergantungan emosional/fisik dapat terjadi pada penggunaan benzodiazepin, termasuk alprazolam. Seperti halnya benzodiazepin lain, risiko ketergantungan meningkat dengan dosis tinggi dan penggunaan jangka panjang, serta semakin tinggi pada pasien dengan riwayat alkoholisme atau penyalahgunaan obat. Penyalahgunaan obat merupakan risiko yang diketahui untuk alprazolam dan benzodiazepin lainnya, sehingga pasien perlu dimonitor secara ketat selama pengobatan. Alprazolam juga berpotensi dalam diversion (diversi) untuk penyalahgunaan. Telah dilaporkan kasus kematian akibat overdosis ketika alprazolam disalahgunakan bersamaan dengan depresan sistem saraf pusat (SSP) lainnya seperti opioid, benzodiazepin lain, dan alkohol. Risiko-risiko ini harus menjadi pertimbangan saat meresepkan atau mendispensasi alprazolam.
Untuk mengurangi risiko, gunakan dosis sekecil mungkin yang sesuai, dan pasien harus diberi edukasi mengenai penyimpanan dan pembuangan sedian yang telah terpakai secara benar.

Perhatian

Sebagai halnya obat-obatan aksi sistem saraf pusat (SSP) lainnya, pasien yang menerima Tablet ATARAX harus diberi peringatan untuk tidak mengoperasikan kendaraan bermotor atau mesin berat sampai diketahui bahwa obat ini tidak menyebabkan kantuk atau pusing selama penggunaan.
Gejala putus obat dapat terjadi setelah penarikan dosis secara cepat atau penghentian mendadak benzodiazepin, termasuk alprazolam. Oleh karena itu, penurunan dosis harus dilakukan secara bertahap untuk mencegah efek samping dari penghentian mendadak. Gejala putus obat dapat berupa disforia ringan dan insomnia, hingga simtom kram perut dan otot, muntah, berkeringat, tremor, dan kejang. Tanda dan gejala ini, terutama yang lebih serius, umumnya lebih sering terjadi pada pasien yang menerima dosis berlebihan dalam jangka waktu lama. Namun, gejala putus obat juga telah dilaporkan pada pasien yang menghentikan benzodiazepin secara tiba-tiba meskipun digunakan dalam dosis terapi. Oleh karena itu, penghentian mendadak harus dihindari dan dosis perlu diturunkan secara bertahap. Jika terapi dihentikan pada pasien dengan gangguan yang berkaitan dengan panik, gejala yang muncul akibat kembalihan serangan panik sering kali menyerupai gejala sindrom putus zat.
Penggunaan pada pasien dengan depresi berat atau risiko bunuh diri harus disertai kehati-hatian yang tepat, termasuk batasan jumlah obat dalam resep. Gangguan panik sering dikaitkan dengan gangguan depresi mayor primer atau sekunder, serta peningkatan risiko bunuh diri pada pasien yang tidak diobati. Maka, kehati-hatian yang sama juga harus diterapkan saat menggunakan dosis tinggi ATARAX untuk pasien dengan gangguan panik, sebagaimana berlaku pada penggunaan obat psikotropika lain untuk pasien depresi atau pasien dengan risiko bunuh diri atau rencana bunuh diri terencana.
Disarankan agar dosis dibatasi pada dosis efektif terkecil, untuk mencegah terjadinya ataksia (gangguan koordinasi otot) atau sedasi berlebihan, yang dapat menjadi masalah khusus pada lansia atau pasien lemah. Kewaspadaan khusus harus diambil ketika menggunakan alprazolam pada pasien dengan gangguan fungsi ginjal atau hati. Berdasarkan efektivitas Tablet ATARAX pada anak-anak di bawah usia 18 tahun belum diketahui.

INTERAKSI OBAT

Benzodiazepin, termasuk alprazolam, dapat memberikan efek aditif depresan SSP (termasuk depresi napas) bila digunakan bersamaan dengan Opioid, Obat psikotropika lain, Obat antikonvulsan, Antihistamin, Alkohol (etanol). Obat lain yang juga menekan sistem saraf pusat.
Konsentrasi plasma imipramine dan desipramine pada keadaan steady state dilaporkan meningkat rata-rata sebesar 31% dan 20%, berturut-turut, akibat pemberian ATARAX Tablet secara bersamaan dalam dosis hingga 4 mg/hari. Signifikansi klinis dari perubahan ini belum diketahui.
Interaksi farmakokinetik dapat terjadi ketika alprazolam diberikan bersama obat-obatan yang mengganggu metabolisme obat tersebut. Senyawa yang menghambat enzim hati tertentu (terutama cytochrome P4503A4) dapat meningkatkan konsentrasi alprazolam dan memperpanjang waktu paruh eliminasi, dan memperkerat efek klinisnya. Namun, setelah paparan ritonavir dalam waktu lama, induksi CYP3A4 mengimbangi penghambatan ini. Interaksi ini memerlukan penyesuaian dosis atau penghentian pemberian alprazolam.
Konsentrasi digoxin yang meningkat telah dilaporkan ketika alprazolam diberikan, terutama pada pasien lansia (>65 tahun). Oleh karena itu, pasien yang menerima alprazolam dan digoxin harus dipantau untuk tanda dan gejala yang terkait dengan toksisitas digoxin.

Karsinogenesis

Tidak ada bukti potensi karsinogenik yang ditemukan selama uji bioassay dua tahun pada tikus dengan dosis hingga 30 mg/kg/hari (150 kali dosis harian manusia yang dianjurkan maksimum sebesar 10 mg/hari) dan pada tikus musang dengan dosis hingga 10 mg/kg/hari (50 kali dosis harian manusia yang dianjurkan maksimum sebesar 10 mg/hari).

Mutagenesis

Alprazolam tidak bersifat mutagenik dalam uji Ames *in vitro*. Alprazolam juga tidak menghasilkan abersi kromosom dalam uji mikronukleus *in vivo* pada tikus dengan dosis tertinggi yang diuji yaitu 100 mg/kg, yang 500 kali lebih besar dari dosis harian manusia yang dianjurkan maksimum sebesar 10 mg/hari. Alprazolam juga tidak bersifat mutagenik *in vitro* dalam uji Kerusakan DNA/Elusi Alkaline.

Fertilitas

Alprazolam tidak menyebabkan gangguan fertilitas pada tikus dengan dosis tertinggi yang diuji yaitu 5 mg/kg/hari, yang 25 kali dosis harian manusia yang dianjurkan maksimum sebesar 10 mg/hari.

Efek Ocular

Tablet ATARAX diberikan perlakuan oral dengan alprazolam pada dosis 3, 10, dan 30 mg/kg/hari (15 hingga 150 kali dosis harian manusia yang dianjurkan maksimum sebesar 10 mg/hari) selama 2 tahun, ditemukan kecenderungan peningkatan jumlah katarak (pada betina) dan vaskularisasi kornea pada jantan yang terkait dengan dosis. Lesi-lesi ini tidak muncul hingga setelah 11 bulan pengobatan.

Efek Obat Anestetik dan Sedatif

Interaksi nonkinis menunjukkan bahwa pemberian obat anestetik dan sedatif yang menghambat reseptor N-metil-D-aspartat