Dr/ Zeinab Tahat

Alzazonex
Extended release Hard gelatin capsules

FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

ALZAZONEX is indicated for the treatment of moderate to severe dementia of the Alzheimer s type.

DOSAGE AND ADMINISTRATION

Recommended Dosing

The dosage of ALZAZONEX shown to be effective in a controlled clinical trial is 28 mg once daily.

The recommended starting dose of ALZAZONEX is 7 mg once daily. The dose should be increased in 7 mg increments to the recommended maintenance dose of 28 mg once daily. The minimum recommended interval between dose increases is one week. The dose should only be increased if the previous dose has been well tolerated. The maximum recommended dose is 28 mg once daily.

ALZAZONEX can be taken with or without food. ALZAZONEX capsules can be taken intact or may be opened, sprinkled on applesauce, and thereby swallowed. The entire contents of each ALZAZONEX capsule should be consumed; the dose should not be divided.

Except when opened and sprinkled on applesauce, as described above, ALZAZONEX should be swallowed whole. ALZAZONEX XR capsules should not be divided, chewed, or crushed.

If a patient misses a single dose of ALZAZONEX, that patient should not double up on the next dose. The next dose should be taken as scheduled. If a patient fails to take ALZAZONEX for several days, dosing may need to be resumed at lower doses and retitrated as described above.

Switching to Alzazonex Capsules

Patients treated with memantine may be switched to Alzazonex capsules as follows:

It is recommended that a patient who is on a regimen of 10 mg twice daily of memantine be switched to Alzazonex 28 mg once daily capsules the day following the last dose of 10 mg memantine. There is no study addressing the comparative efficacy of these 2 regimens.

Dosing in Patients with Renal Impairment

In patients with severe renal impairment (creatinine clearance of 5 – 29 mL/min, based on the Cockcroft-Gault equation), the recommended maintenance dose (and maximum recommended dose) is 14 mg/day *[see Clinical Pharmacology]*.

DOSAGE FORMS AND STRENGTHS

Dosage form: Extended release hard gelatin capsules with opaque white cap and opaque white body , each capsule contains 10 % SR memantine hydrochloride pellets 280 mg containing 28 mg memantine Hydrochloride

Strength : 28 mg

CONTRAINDICATIONS

ALZAZONEX is contraindicated in patients with known hypersensitivity to memantine

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hydrochloride or to any excipients used in the formulation.

WARNINGS AND PRECAUTIONS

Genitourinary Conditions

Conditions that raise urine pH may decrease the urinary elimination of memantine resulting in increased plasma levels of memantine *[see Drug Interactions (7.1)]*.

The most common adverse reaction that led to treatment discontinuation in ALZAZONEX group was dizziness

Adverse Reaction :

Gastrointestinal Disorders: Diarrhea , Constipation, Abdominal pain , Vomiting .
Infections and Infestations: Influenza
Investigations :Weight, increased
Musculoskeletal and Connective Tissue Disorders: Back pain
Nervous System Disorders : Headache , Dizziness ,Somnolence
Psychiatric Disorders: Anxiety ,Depression , Aggression
Renal and Urinary Disorders :Urinary incontinence
Vascular Disorders :Hypertension ,Hypotension

ADVERSE REACTIONS

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of memantine. Because these reactions are reported voluntarily from a population of Uncertain size, it is not always possible to reliably estimate their frequency or establish a Causal relationship to drug exposure. These reactions include:

Blood and Lymphatic System Disorders: agranulocytosis, leukopenia (including neutropenia), pancytopenia, thrombocytopenia, thrombotic thrombocytopenic purpura.

Cardiac Disorders: cardiac failure congestive.

Gastrointestinal Disorders: pancreatitis.

Hepatobiliary Disorders: hepatitis.

Psychiatric Disorders: suicidal ideation.

Renal and Urinary Disorders: acute renal failure (including increased creatinine and renal Insufficiency).

Skin Disorders: Stevens Johnson syndrome.

DRUG INTERACTIONS

Drugs That Make Urine Alkaline

The clearance of memantine was reduced by about 80% under alkaline urine conditions at pH 8. Therefore, alterations of urine pH towards the alkaline condition may lead to an accumulation of the drug with a possible increase in adverse effects. Urine pH is altered by diet, drugs (e.g. carbonic anhydrase inhibitors, sodium bicarbonate) and clinical state of the patient (e.g. renal tubular acidosis or severe infections of the urinary tract). Hence, memantine should be used with caution under these conditions.

Use with Other N-methyl-D-aspartate (NMDA) Antagonists

The combined use of ALZAZONEX with other NMDA antagonists (amantadine, ketamine, and dextromethorphan) has not been systematically evaluated and such use should be approached with caution.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no adequate data on the developmental risk associated with the use of ALZAZONEX in pregnant women.

Adverse developmental effects (decreased body weight and skeletal ossification) were observed in the offspring of rats administered memantine during pregnancy at doses associated with minimal maternal toxicity. These doses are higher than those used in humans at the maximum recommended daily dose of ALZAZONEX *[see Data]*.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Data

Lactation

Risk Summary

There are no data on the presence of memantine in human milk, the effects on the breastfed infant, or the effects of ALZAZONEX on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mothers clinical need for ALZAZONEX and any potential adverse effects on the Breastfed infant from ALZAZONEX or from the underlying maternal condition.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established

Geriatric Use

The majority of people with Alzheimer's disease are 65 years of age and older. In the clinical study of memantine hydrochloride extended-release, the mean age of patients was approximately 77 years; over 91% of patients were 65 years and older, 67% were 75 years and older, and 14% were at or above 85 years of age. The efficacy and safety data presented in the clinical trial sections were obtained from these patients. There were no clinically meaningful differences in most adverse reactions reported by patient groups ≥ 65 years old and < 65 years old

Renal Impairment

No dosage adjustment is needed in patients with mild or moderate renal impairment. A dosage reduction is recommended in patients with severe renal impairment *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*.

Hepatic Impairment

No dosage adjustment is needed in patients with mild or moderate hepatic impairment. Alzazonex was not studied in patients with severe hepatic impairment *[see Clinical Pharmacology (12.3)]*.

OVERDOSAGE

Signs and symptoms most often accompanying overdosage with other formulations of memantine in clinical trials and from worldwide marketing experience, alone or in combination with other drugs and/or alcohol, include agitation, asthenia, bradycardia, confusion, coma, dizziness, ECG changes, increased blood pressure, lethargy, loss of consciousness, psychosis, restlessness, slowed movement, somnolence, stupor, unsteady gait, visual hallucinations, vertigo, vomiting, and weakness. The largest known ingestion

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of memantine worldwide was 2 grams in a patient who took memantine in conjunction with unspecified antidiabetic medications. This patient experienced coma, diplopia, and agitation, but subsequently recovered.

Fatal outcome has been very rarely reported with memantine, and the relationship to memantine was unclear.

Because strategies for the management of overdose are continually evolving, it is advisable to contact a poison control center to determine the latest recommendations for the management of an overdose of any drug. As in any cases of overdose, general supportive measures should be utilized, and treatment should be symptomatic.

Elimination of memantine can be enhanced by acidification of urine

DESCRIPTION

ALZAZONEX (memantine hydrochloride) is an orally active NMDA receptor antagonist.

ALZAZONEX capsules are supplied for oral administration 28 mg capsules.

Each E.R.H.G.Caps contains 10% SR memantine hydrochloride pellets 280 mg containing memantine hydrochloride 28 mg

inactive ingredients: NP seeds (Non pariel seeds)
Polyvinyl pyrolidone K30
Polysorbate 80
Diethyl phthalate
Hypromellose 5cp
Isopropyl alcohol

Methylene chloride

N.B: NP seeds contain: Pharma grade sugar , starch , Hypromellose 5 cp, Povidone k30

Each capsule shell contain
Gelatin
Methyl paraben
Propyl Paraben
Sodium lauryl sulphate
Aerosol
Titanium dioxide
Red iron oxide

CLINICAL PHARMACOLOGY

Mechanism of Action

Persistent activation of central nervous system N-methyl-D-aspartate (NMDA) receptors by the excitatory amino acid glutamate has been hypothesized to contribute to the symptomatology of Alzheimer's disease. Memantine is postulated to exert its therapeutic effect through its action as a low to moderate affinity uncompetitive (open-channel) NMDA receptor antagonist which binds preferentially to the NMDA receptor-operated cation channels. There is no evidence that memantine prevents or slows neurodegeneration in patients with Alzheimer's disease.

Pharmacodynamics

Memantine showed low to negligible affinity for GABA, benzodiazepine, dopamine, adrenergic, histamine and glycine receptors and for voltage-dependent Ca2+, Na+, or K+

channels. Memantine also showed antagonistic effects at the 5HT3 receptor with a potency similar to that for the NMDA receptor and blocked nicotinic acetylcholine receptors with one-sixth to one-tenth the potency.
In vitro studies have shown that memantine does not affect the reversible inhibition of acetylcholinesterase by donepezil, galantamine, or tacrine.

Pharmacokinetics
Memantine is well absorbed after oral administration and has linear pharmacokinetics over the therapeutic dose range. It is excreted predominantly unchanged in urine and has a terminal elimination half-life of about 60-80 hours. In a study comparing 28 mg once daily ALZAZONEX XR to 10 mg twice daily ALZAZONEX, the Cmax and AUC0-24 values were 48% and 33% higher for the XR dosage regimen, respectively.
Absorption
After multiple dose administration of ALZAZONEX XR, memantine peak concentrations occur around 9-12 hours post-dose. There is no difference in the absorption of ALZAZONEX XR when the capsule is taken intact or when the contents are sprinkled on applesauce.
There is no difference in memantine exposure, based on Cmax or AUC, for ALZAZONEX XR whether that drug product is administered with food or on an empty stomach. However, peak plasma concentrations are achieved about 18 hours after administration with food versus approximately 25 hours after administration on an empty stomach
Distribution
The mean volume of distribution of memantine is 9-11 L/kg and the plasma protein binding is low (45%).
Elimination
Metabolism
Memantine undergoes partial hepatic metabolism. The hepatic microsomal CYP450 enzyme system does not play a significant role in the metabolism of memantine.
Excretion
Memantine is excreted predominantly unchanged in the urine and has a terminal elimination half-life of about 60-80 hours. About 48% of administered drug is excreted unchanged in urine; the remainder is converted primarily to three polar metabolites which possess minimal NMDA receptor antagonistic activity: the N-glucuronide conjugate, 6-hydroxy-memantine, and 1-nitroso-deaminated memantine. A total of 74% of the administered dose is excreted as the sum of the parent drug and the N-glucuronide conjugate. Renal clearance involves active tubular secretion moderated by pH dependent tubular reabsorption.
Specific Populations
Elderly
The pharmacokinetics of memantine in young and elderly subjects are similar.
Gender
Following multiple dose administration of memantine hydrochloride20 mg daily, females had about 45% higher exposure than males, but there was no difference in exposure when body weight was taken into account.
Renal Impairment
Memantine pharmacokinetics were evaluated following single oral administration of 20

mg memantine hydrochloride in 8 subjects with mild renal impairment (creatinine clearance, CLcr, > 50 – 80 mL/min), 8 subjects with moderate renal impairment (CLcr 30 – 49 mL/min), 7 subjects with severe renal impairment (CLcr 5 – 29 mL/min) and 8 healthy subjects (CLcr > 80 mL/min) matched as closely as possible by age, weight and gender to the subjects with renal impairment. Mean AUC0-· increased by 4%, 60%, and 115% in subjects with mild, moderate, and severe renal impairment, respectively, compared to healthy subjects. The terminal elimination half-life increased by 18%, 41%, and 95% in subjects with mild, moderate, and severe renal impairment, respectively, compared to healthy subjects.

Hepatic Impairment
Memantine pharmacokinetics were evaluated following the administration of single oral doses of 20 mg in 8 subjects with moderate hepatic impairment (Child-Pugh Class B, score 7-9) and 8 subjects who were age-, gender-, and weight-matched to the hepatically impaired subjects. There was no change in memantine exposure (based on Cmax and AUC) in subjects with moderate hepatic impairment as compared with healthy subjects. However, terminal elimination half-life increased by about 16% in subjects with moderate hepatic impairment as compared with healthy subjects.
Drug-Drug Interactions
Use with Cholinesterase Inhibitors
Coadministration of memantine with the AChE inhibitor donepezil did not affect the pharmacokinetics of either compound. Furthermore, memantine did not affect AChE inhibition by donepezil. In a 24-week controlled clinical study in patients with moderate to severe Alzheimer's disease, the adverse reaction profile observed with a combination of memantine immediate-release and donepezil was similar to that of donepezil alone.
Effect of Memantine on the Metabolism of Other Drugs
In vitro studies conducted with marker substrates of CYP450 enzymes (CYP1A2, -2A6, -2C9, -2D6, -2E1, -3A4) showed minimal inhibition of these enzymes by memantine. In addition, *in vitro* studies indicate that at concentrations exceeding those associated with efficacy, memantine does not induce the cytochrome P450 isozymes CYP1A2, -2C9, -2E1 and -3A4/5. No pharmacokinetic interactions with drugs metabolized by these enzymes are expected.
Pharmacokinetic studies evaluated the potential of memantine for interaction with warfarin and bupropion. Memantine did not affect the pharmacokinetics of the CYP2B6 substrate bupropion or its metabolite hydroxybupropion. Furthermore, memantine did not affect the pharmacokinetics or pharmacodynamics of warfarin as assessed by the prothrombin INR.
Effect of Other Drugs on Memantine
Memantine is predominantly renally eliminated, and drugs that are substrates and/or inhibitors of the CYP450 system are not expected to alter the metabolism of memantine.
Drugs Eliminated via Renal Mechanisms
Because memantine is eliminated in part by tubular secretion, coadministration of drugs that use the same renal cationic system, including hydrochlorothiazide (HCTZ),

triamterene (TA), metformin, cimetidine, ranitidine, quinidine, and nicotine, could potentially result in altered plasma levels of both agents. However, coadministration of memantine and HCTZ/TA did not affect the bioavailability of either memantine or TA, and the bioavailability of HCTZ decreased by 20%. In addition, coadministration of memantine with the antihyperglycemic drug Glucovance· (glyburide and metformin hydrochloride) did not affect the pharmacokinetics of memantine, metformin and glyburide. Furthermore, memantine did not modify the serum glucose lowering effect of Glucovance ,indicating the absence of a pharmacodynamic interaction.

Drugs Highly Bound to Plasma Proteins

Because the plasma protein binding of memantine is low (45%), an interaction with drugs that are highly bound to plasma proteins, such as warfarin and digoxin, is unlikely.

HOW SUPPLIED/STORAGE AND HANDLING

Physical characters : hard gelatin capsules of opaque white cap & opaque white body containing white to off white pellets

Carton box containing 1,2 or 3 (Al/ transparent PVC) strips each of 10 extended release hard gelatin capsules

Storage

Store at temperature not exceeding 30 °C, in dry place

Shelf life : 24 months

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

• To assure safe and effective use of ALZAZONEX, the information and instructions provided in the patient information section should be discussed with patients and caregivers.

• Instruct patients and caregivers to take ALZAZONEX only once per day, as prescribed.

• Instruct patients and caregivers that ALZAZONEX capsules be swallowed whole. Alternatively, ALZAZONEX capsules may be opened and sprinkled on applesauce and the entire contents should be consumed. The capsules should not be divided, chewed or crushed.

• Warn patients not to use any capsules of ALZAZONEX that are damaged or show signs of tampering.

• If a patient misses a single dose of ALZAZONEX, that patient should not double up on the next dose. The next dose should be taken as scheduled. If a patient fails to take ALZAZONEX for several days, dosing should not be resumed without consulting that patient's healthcare professional.

• Advise patients and caregivers that ALZAZONEX XR may cause headache, diarrhea, and dizziness.

Manufactured by: DBK pharma for pharmaceutical industries (DBK pharma) for Zeta Pharma for Pharmaceutical industries

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ألزازونكس كبسولات جيلاتينية صلبة ممتدة المفعول

أقرا نشرة الدواء التى تأتى مع ألزازونيكس قبل البدء في تناول الدواء
وفي كل مرة تحصل على العبوة. قد تكون هناك معلومات جديدة.
هذه المعلومات لا تأخذ مكان التحدث مع طبيبك حول حالتك الصحية وطريقة علاجك

ما هو ألزازونكس ؟

يستخدم الزازونكس لعلاج حالات الخرف المتوسطة إلى الشديدة عند المرضى المصابين بالزهايمر , ألزازونكس ينتمى إلى مجموعة أدوية تسمى مثبطات N-methyl-D-aspartate (NMDA)
من غير المعروف إذا كان ألزازونكس آمن وفعال فى الأطفال

من لا ينبغى أن يأخذ ألزازونكس ؟

لا ينبغى أن تتناول ألزازونكس إذا كان لديك حساسية من ميمانتين أو أى من مكونات الدواء الأخرى (أنظر نهاية النشرة لتحصل على قائمة كاملة من مكونات ألزازونكس)

ماذا يجب أن أخبر الطبيب قبل أخذ ألزازونكس ؟

قبل أن تأخذ ألزازونكس

أخبر طبيبك إذا :

• كان لديك أو كنت تعانى من نوبات
• كان لديك أو كنت تعانى من مشاكل فى التبول
• كان لديك أو كنت تعانى من مشاكل فى المثانة أو الكلى
• لديك مشاكل فى الكبد
• لديك أي حالات طبية أخرى
• إذا كنتى حامل أو تخططين للحمل من غير المعروف إذا كان ألزازونكس سوف يؤذى طفلك الذى لم يولد بعد أم لا
• إذا كنتى مرضعة أو تخططين للرضاعة من غير المعروف إذا كان ألزازونكس ينتقل إلى حليب الثدى أو لا
تحدثى إلى طبيبك حول أفضل طريقة لإطعام طفلك خاصة إذا تناولتى ألزازونكس
أخبر طبيبك عن جميع الأدوية التي تتناولها ، بما في ذلك الوصفات الطبية وغير الموصوفة الأدوية والفيتامينات والمكملات العشبية.
قد يؤثر تناول ألزازونكس مع بعض الأدوية الأخرى على بعضها البعض مع الأخذ أنه من الممكن أن يسبب أثار جانبية خطيرة مع الأدوية الأخرى

أخبر طبيبك بشكل خاص إذا كنت تتناول:

مضادات NMDA الأخرى مثل ketamine , amantadine, dextromethorphan
الأدوية التي تجعل البول قلويًا مثل مثبطات الأنهيدراز الكربوني و بيكربونات الصوديوم

اسأل طبيبك أو الصيدلي عن قائمة بهذه الأدوية ، إذا لم تكن متأكدًا.
تعرف على الأدوية التي تتناولها. احتفظ بقائمة بها لعرضها على طبيبك والصيدلي
عندما تحصل على دواء جديد

كيف يجب أن أتناول ألزازونكس ؟

سيخبرك طبيبك بكمية ألزازونكس التى يجب أن تتناولها ومتى تأخذها
قد يغير الطبيب الجرعة إذا لزم الأمر
يمكن تناول ألزازونكس مع الطعام أو بدونه
يمكن فتح كبسولات ألزازونكس ورشها على عصير التفاح قبل البلع ولكن يجب تناول محتويات الكبسولة بأكملها والجرعه لا ينبغى تقسيمها قبل الفتح والرش على عصير التفاح
يجب إبتلاع كبسولات ألزازونكس كاملة وعدم سحقها أو تقسيمها

لا تستخدم كبسولات ألزازونكس تالفة أو تظهر عليها علامات العبث
إذا كنت تتناول حاليا تركيبة أخرى من ميمانتين فتحدث إلى مسئول رعايتك الصحية حول كيفية التبديل إلى ألزازونكس
إذا نسيت جرعة واحدة من ألزازونكس فلا تضاعف الجرعة الثانية يجب أن تأخذ الجرعة الثانية كما هو مقرر
إذا نسيت تناول ألزازونكس لعدة أيام فلا يجب تناول الجرعة الثانية حتى تتحدث مع طبيبك
إذا كنت تتناول الكثير من ألزازونكس فاتصل بطبيبك أو أقرب مركز سموم أو اذهب إلى أقرب غرفة مستشفى طوارئ على الفور

ماهى الأثار الجانبية المحتملة لألزازونكس ؟
قد يسبب ألزازونكس أثارا جانبية بما فى ذلك
تسمل الأثار الجانبية الأكثر شيوعا لألزازونكس ما يلى :
- صداع الراس
- إسهال
- دوار

هذه ليست كل الأثار الجانبية المحتملة لألزازونكس , لمزيد من المعلومات أسأل طبيبك أو الصيدلي , يمكنك إستدعاء الطبيب للحصول على المشورة الطبية حول الأثار الجانبية
يمكنك الإبلاغ عن الأثار الجانبية عن طريق البريد الإلكترونى Pv@zeta-pharma.com أو عن طريق الموقع الإلكترونى www.zetapharma.net

كيف يمكن تخزين ألزازونكس ؟
يتم التخزين فى درجة حرارة لاتتجاوز 30 درجة منوية , فى مكان جاف , يحفظ بعيدا عن متناول الأطفال
مدة الصلاحية:24 شهر

ماهى مكونات ألزازونكس ؟
المواد الفعالة : ميمانتين هيدروكلوريد كل كبسولة جيلاتينية صلبة تحتوى على حبيبات ميمانتين هيدروكلوريد (10 %) ويكافئ 28 مجم من ميمانتين هيدروكلوريد
المواد الغير فعالة : بذور غير باريليه (سكر,نشا, هيبر ميلوز, بوفيدون K30), بوفيدون , بولى سوربات 80 , دى إيثيل فثالات , هيبرميلوز , كحول, ميثيلين كلوريد
مكونات الكبسولة : جيلاتين , ميثيل بارابين , بروبيل بارابين , كبريتات لوريل الصوديوم , إيروسيل , تيتانيوم دى أوكسيد (CI 77891) , أوكسيد الحديد الأحمر (CI 77491)
عبوة كرتون تحتوى على 1 , 2 , أو 3 شرائط (Al/ transparent PVC) كل شريط يحتوى على 10 كبسولات جيلاتينية صلبة ممتدة المفعول

معلومات عامة عن الإستخدام الأمن والفعال لألزازونكس

توصف الأدوية أحيانا لأغراض أخرى غير تلك المدرجة فى نشرة معلومات المريض لا تأخذ ألزازونكس لحالة غير منصوص عليها فى نشرة معلومات المريض لا تعطى ألزازونكس لأشخاص أخرين حتى لو كان لديهم نفس الشئ لأنه قد يضرهم

تلخص نشرة معلومات المريض أهم المعلومات حول ألزازونكس إذا كنت ترغب فى مزيد من المعلومات تحدث إلى طبيبك أو الصيدلى للحصول على معلومات حول ألزازونكس الذى تمت كتابته عن طريق متخصصو الرعاية الصحية

لمزيد من المعلومات حول ألزازونكس أنتقل إلى www.zetapharma.net أو إتصل على 022715582

تم التصنيع بواسطة شركة دى بى كى فارما للصناعات الدوائية لصالح شركة زيتا فارما للصناعات الدوائية