UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K

CURRENT REPORT

Pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934

Date of report (date of earliest event reported): July 24, 2023

TONIX PHARMACEUTICALS HOLDING CORP.

(Exact name of registrant as specified in its charter)

Nevada	**001-36019**	**26-1434750**
(State or Other Jurisdiction of Incorporation)	**(Commission File Number)**	**(IRS Employer Identification No.)**

26 Main Street, Chatham, New Jersey 07928
(Address of principal executive offices) (Zip Code)

Registrant's telephone number, including area code: (862) 904-8182

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions (see General Instruction A.2. below):

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)
☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)
☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))
☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock	TNXP	The NASDAQ Capital Market

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§ 230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§ 240.12b-2 of this chapter).

Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 7.01 Regulation FD Disclosure.

On July 24, 2023, Tonix Pharmaceuticals Holding Corp. (the "Company") announced data supporting the memory- and cognition-enhancing effects of its TNX-601 ER (tianeptine hemioxalate extended release) and TNX-4300 (estianeptine), the single *(S)*-isomer of tianeptine, product candidates. A copy of the press release which discusses this matter is furnished hereto as Exhibit 99.01, and incorporated herein by reference.

The information in this Item 7.01 of this Current Report on Form 8-K, including Exhibit 99.01 attached hereto, shall not be deemed "filed" for purposes of Section 18 of the United States Securities Exchange Act of 1934 (the "Exchange Act") or otherwise subject to the liabilities of that section, nor shall they be deemed incorporated by reference in any filing under the United States Securities Act of 1933 or the Exchange Act, except as shall be expressly set forth by specific reference in such a filing.

Item 8.01. Other Events.

On July 24, 2023, the Company announced data supporting the memory- and cognition-enhancing effects of TNX-601 ER and TNX-4300. The findings reported today show that tianeptine and estianeptine improve memory and cognition as measured in the rat Novel Object Recognition ("NOR") test. The finding that estianeptine is responsible for improving memory and cognition suggests a role for PPAR-β/δ activation in memory. The memory- and cognition-enhancing effects of racemic tianeptine and estianeptine seen in the NOR test are consistent with human clinical studies in which racemic tianeptine treatment improved cognition and memory in patients with Alzheimer's disease and depression and in patients with bipolar disorder. The Company believes these findings support the development of tianeptine and estianeptine in psychiatric and neurodegenerative diseases.

The Company believes its ongoing clinical studies in major depression on TNX-601 ER, which contains racemic tianeptine, are expected to inform and potentially accelerate the development of TNX-4300 which contains the single isomer, estianeptine. The Company believes that estianeptine bypasses the synapse and activates intracellular PPAR-β/δ and PPAR-γ targets. The finding that estianeptine is responsible for tianeptine's ability to improve memory and cognition in the NOR test implicates PPAR-β/δ activation specifically as a molecular target. This finding is consistent with the impaired memory of mice lacking the PPAR-β/δ gene. In depression, estianeptine is believed to act on PPAR-β/δ and PPAR-γ targets in the nucleus to enhance genetic transactivation involved in restoring hippocampal neuroplasticity and neurogenesis. The Company believes these findings have applicability to neurodegenerative diseases in which neuronal connections are atrophied. The reported PPAR mechanism has potential relevance to why tianeptine is not associated with sexual dysfunction, weight gain or several other treatment-limiting toxicities, which are associated with the antidepressants

currently marketed in the U.S. for long-term use.

Forward- Looking Statements

This Current Report on Form 8-K contains certain forward-looking statements within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934 and Private Securities Litigation Reform Act, as amended, including those relating to the Company's product development, clinical trials, clinical and regulatory timelines, market opportunity, competitive position, possible or assumed future results of operations, business strategies, potential growth opportunities and other statement that are predictive in nature. These forward-looking statements are based on current expectations, estimates, forecasts and projections about the industry and markets in which we operate and management's current beliefs and assumptions.

These statements may be identified by the use of forward-looking expressions, including, but not limited to, "expect," "anticipate," "intend," "plan," "believe," "estimate," "potential," "predict," "project," "should," "would" and similar expressions and the negatives of those terms. These statements relate to future events or our financial performance and involve known and unknown risks, uncertainties, and other factors which may cause actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements. Such factors include those set forth in the Company's filings with the SEC. Prospective investors are cautioned not to place undue reliance on such forward-looking statements, which speak only as of the date of this press release. The Company undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise.

Item 9.01 Financial Statements and Exhibits.

(d)

Exhibit No.	Description.
99.01	Press Release of the Company, dated July 24, 2023
104	Cover Page Interactive Data File (embedded within the Inline XBRL document)

SIGNATURE

Pursuant to the requirement of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned thereunto duly authorized.

TONIX PHARMACEUTICALS HOLDING CORP.

Date: July 24, 2023

By: /s/ Bradley Saenger
Bradley Saenger
Chief Financial Officer

Exhibit 99.01

Tonix Pharmaceuticals Announces Data Supporting the Memory- and Cognition-Enhancing Effects of Racemic Tianeptine and *(S)*-Tianeptine, but not *(R)*-Tianeptine, in the *In Vivo* Rat Novel Object Recognition (NOR) Test

New Findings Support Development of Racemic Tianeptine and (S)-Tianeptine (Estianeptine) as First-in-Class Oral Therapies in Alzheimer's Disease and Other Psychiatric and Neurodegenerative Conditions with Memory Deficits

(S)-Tianeptine Effects on Novel Object Recognition are Consistent with a Role for PPAR-β/δ Activation in Improving Memory and Cognition

Topline Results Expected First Quarter 2024 from the Currently Enrolling Potentially Pivotal Phase 2 UPLIFT Study of TNX-601 ER (Racemic Tianeptine) in Major Depressive Disorder

CHATHAM, N.J., July 24, 2023 – Tonix Pharmaceuticals Holding Corp. (Nasdaq: TNXP) (Tonix or the Company), a biopharmaceutical company, today announced data supporting the memory- and cognition-enhancing effects of two Tonix drug candidates, TNX-601 ER (tianeptine hemioxalate extended release) and TNX-4300 (estianeptine), the single *(S)*-isomer of tianeptine. TNX-601 ER is being tested in the potentially pivotal Phase 2 UPLIFT [1] trial for the treatment of major depressive disorder (MDD), with topline results expected in the first quarter of 2024. TNX-4300 is in preclinical development for mood disorders, Alzheimer's disease and Parkinson's disease.* The findings reported today show that tianeptine and estianeptine improve memory and cognition as measured in the rat Novel Object Recognition (NOR) test. The finding that estianeptine is responsible for improving memory and cognition suggests a role for PPAR-β/δ activation in memory.

Tianeptine is an antidepressant that has been marketed outside the U.S. for more than 30 years. Tianeptine is also a racemic drug composed of a 1:1 mixture of two mirror-image isomers. Tonix recently reported that the *(S)*-isomer (estianeptine) is responsible for its positive effects on neuroplasticity in cell culture, while the *(R)*-isomer is responsible for racemic tianeptine's off-target activity on the μ-opioid receptor. [2,3] Tonix also recently reported that estianeptine activates peroxisome proliferator-activated receptors PPAR-β/δ and PPAR-γ. These activities on molecular targets in neurons and glia in the brain are believed to relate to tianeptine's ability to restore connectivity between neurons that atrophy in conditions of stress or depression in animal models.[4] Tianeptine's mechanism is distinct from traditional antidepressants that alter the level or activity of serotonin, norepinephrine, and dopamine neurotransmitters, which are believed to indirectly induce neurons to make new connections.[5]

"The memory- and cognition-enhancing effects of racemic tianeptine and estianeptine seen in the NOR test are consistent with human clinical studies in which racemic tianeptine treatment improved cognition and memory in patients with Alzheimer's disease and depression[6] and in patients with bipolar disorder, [7]" said Seth Lederman, M.D., Chief Executive Officer of Tonix Pharmaceuticals. "We recently reported that estianeptine induces neuroplasticity in cell culture.[2] The new findings indicate that estianeptine also improves memory and cognition in the *in vivo* rat NOR test. We believe that together these findings support the development of tianeptine and estianeptine in psychiatric and neurodegenerative diseases. Tianeptine's ability to restore atrophied neuronal connections in animals[2] suggests the potential to achieve durable outcomes."

"The rat NOR test is an experimental tool to assess drug effects on memory and evaluate their potential as treatments for neurodegenerative conditions like Alzheimer's disease," said Gregory Sullivan, M.D., Chief Medical Officer of Tonix Pharmaceuticals. "Since t he main initial clinical feature in Alzheimer's disease is impairment in newly learned facts or memories, improving learning and memory are important properties of potential new therapeutics. The specific type of learning and recognition memory measured by the NOR is believed to be relevant to the neurocircuitry impaired in Alzheimer's disease."

Dr. Sullivan continued, "Our ongoing clinical studies in major depression on TNX-601 ER, which contains racemic tianeptine, are expected to inform and potentially accelerate the development of TNX-4300 which contains the single isomer, estianeptine. We believe that estianeptine bypasses the synapse and activates intracellular PPAR-β/δ and PPAR-γ targets. The finding that estianeptine is responsible for tianeptine's ability to improve memory and cognition in the NOR test implicates PPAR-β/δ activation specifically as a molecular target. This finding is consistent with the impaired memory of mice lacking the PPAR-β/δ gene."[8]

In depression, estianeptine is believed to act on PPAR-β/δ and PPAR-γ targets in the nucleus to enhance genetic transactivation involved in restoring hippocampal neuroplasticity and neurogenesis. These findings also have applicability to neurodegenerative diseases in which neuronal connections are atrophied.[2] The reported PPAR mechanism has potential relevance to why tianeptine is not associated with sexual dysfunction, weight gain or several other treatment-limiting toxicities associated with the antidepressants currently marketed in the U.S. for long-term use. However, tianeptine has other potential side effects that are described in its labeling outside the U.S. where it is marketed as a prescription drug.

Tonix owns worldwide rights to the novel salt, racemic tianeptine hemioxalate and to the proprietary extended-release formulation employed in TNX-601 ER that allows once daily dosing. TNX-601 ER is currently being studied in the Phase 2 UPLIFT trial, which is targeting enrollment of approximately 300 patients at about 30 U.S. clinical sites. Tonix has also filed patents claiming single *(S)*-isomer estianeptine, the active ingredient in TNX-4300, which is devoid of activity on the μ-opioid receptor. TNX-4300 is currently in preclinical development for depression, bipolar disorder, Alzheimer's disease, and Parkinson's disease.

Key experiments were performed by scientists at Tonix's Research and Development Center (RDC) in Frederick, Maryland.

*TNX-601 ER and TNX-4300 are investigational new drugs and are not approved for any indication. TNX-601 ER is being developed under an IND. TNX-4300 is at the pre-IND stage of development.

About Tianeptine

Racemic tianeptine sodium (amorphous) immediate release (dosed 3 times daily) was first marketed for depression in France in 1989 and has been available for decades in Europe, Russia, Asia, and Latin America for the treatment of depression. Tianeptine sodium has an established tolerability profile from decades of use in these jurisdictions. Currently no tianeptine-containing product is approved in the U.S. and no extended-release once-daily tianeptine product is approved in any jurisdiction. In animal models, tianeptine restores dendritic arborization of pyramidal neurons in the CA3 region of hippocampus and in the dentate gyrus region promotes new neuron formation and integration into hippocampal networks.[4] Tianeptine's enhancement of neuroplasticity in animal models of stress is believed to be mediated by activation of PPAR isoforms PPAR-β/δ and PPAR-γ, which is mechanistically distinct from traditional monoaminergic antidepressants marketed in the U.S. and contributes to its potential for clinical indications beyond depression and stress disorders. Tianeptine and its MC5 metabolite are also weak μ-opioid receptor (MOR) agonists that present a potential abuse liability if illicitly misused in large quantities. [3,9] In cases where tianeptine has been abused, the dose has been approximately 8-80 times the therapeutic dose in depression on a daily basis.[9] In patients who were prescribed tianeptine for depression, the French Transparency Committee found an incidence of misuse of approximately 1 case per 1,000 patients treated[9] suggesting low abuse liability when used at the antidepressant dose in patients prescribed tianeptine for depression. Clinical trials have shown that cessation of a therapeutic course of tianeptine does not appear to result in dependence or withdrawal symptoms following 6-weeks[11-15], 3-months,[16] or 12-months[17] of treatment. Estianeptine is believed to mimic naturally occurring polyunsaturated fatty acid ligands in low affinity interactions with PPAR-β/δ and PPAR-γ. Estianeptine's activation of nuclear PPAR-β/δ and PPAR-γ receptors appears to be a more direct mechanism to achieve the goal of restoring neuronal connectivity than the active ingredients of current pharmacologic therapies for depression. Tianeptine's proposed mechanism as a plastogen is consistent with its clinical effects in promoting cognition in depressed patients with Alzheimer's disease[5] and in patients with bipolar disorder. [6] The PPAR-β/δ target is validated by prior work on agonists treating animal models of neurodegenerative and autoimmune diseases of the central nervous system.[18] Alzheimer's disease has been proposed to be a form of diabetes that affects the CNS, sometimes termed type-III diabetes."[19] The PPAR superfamily plays key roles in metabolic processes, and activation of PPAR-β/δ in brain by tianeptine shows promise to prevent the cognitive dysfunction associated with CNS insulin resistance. Tianeptine's reported pro-cognitive and anxiolytic effects as well as its ability to attenuate the neuropathological effects of excessive stress responses suggest other potential uses including as a treatment for posttraumatic stress disorder (PTSD), as well as for preventing neurocognitive dysfunction associated with corticosteroid use.

About the Novel Object Recognition Test (NOR)

NOR is one of several cognitive tests that engage working memory and is considered a model for testing therapeutics or co-factors for Alzheimer's disease. [20] The NOR task depends on the accurate comparison of novel information with recently stored memories. Among animal behavioral models for assessing cognitive functioning, the NOR test measures a specific form of recognition memory without assumptions about drug mechanism. The NOR is based on the spontaneous behavior of rodents without the need for external motivation, reward, or punishment. Impairments of NOR are seen in many animal models, including mice that overexpress the amyloid protein associated with Alzheimer's disease.[21] The NOR tests on tianeptine and estianeptine were performed by a third-party contract research organization. In the NOR test, rats were assessed for cognitive ability in a test apparatus comprising an open-field arena and were scored by an observer blind to treatments. The positive control for a drug effect was the acetylcholinesterase inhibitor medication galantamine, which is the active ingredient of Razadyne®, approved by the U.S. Food and Drug administration as a treatment for Alzheimer's disease. On Days 1 and 2, rats were allowed to freely explore the empty arena for a 10-minute habituation period. On Day 3, rats were administered saline, galantamine or test article (racemic tianeptine or estianeptine) and following the pretreatment time of 60 min, rats were then placed into the test arena in the presence of two identical objects. The time spent actively exploring the objects during a 3-minute training (T1) session was recorded. Each rat was returned to its home cage following training. After 48 hours, the rats were administered saline, galantamine or test article again, and, after 60 min, they were placed into the test arena in the presence of two objects: one familiar and one novel. The times spent exploring each object were recorded for 5 minutes in the testing session (T2). The outcome measure known as the Recognition Index was employed in these studies, defined as the ratio of the time spent exploring the novel object over the total time spent exploring both objects. These results are being prepared for presentation at a scientific meeting and for publication.

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Tonix Pharmaceuticals Holding Corp.*

Tonix is a biopharmaceutical company focused on commercializing, developing, discovering and licensing therapeutics to treat and prevent human disease and alleviate suffering. Tonix markets Zembrace® SymTouch® (sumatriptan injection) 3 mg and Tosymra® (sumatriptan nasal spray) 10 mg. Zembrace SymTouch and Tosymra are each indicated for the treatment of acute migraine with or without aura in adults. Tonix's development portfolio is composed of central nervous system (CNS), rare disease, immunology and infectious disease product candidates. Tonix's CNS development portfolio includes both small molecules and biologics to treat pain, neurologic, psychiatric and addiction conditions. Tonix's lead CNS candidate, TNX-102 SL (cyclobenzaprine HCl sublingual tablet), is in mid-Phase 3 development for the management of fibromyalgia with topline data expected in the first quarter of 2024. TNX-102 SL is also being developed to treat Long COVID, a chronic post-acute COVID-19 condition. Enrollment in a Phase 2 study has been completed, and topline results are expected in the third quarter of 2023. TNX-601 ER (tianeptine hemioxalate extended-release tablets), a once-daily formulation being developed as a treatment for major depressive disorder (MDD), is also currently enrolling with topline results expected in the first quarter of 2024. TNX-4300 (estianeptine) is a small molecule oral therapeutic in preclinical development to treat MDD, Alzheimer's disease and Parkinson's disease. TNX-1900 (intranasal potentiated oxytocin), in development for chronic migraine, is currently enrolling with topline data expected in the fourth quarter of 2023. TNX-1300 (cocaine esterase) is a biologic designed to treat cocaine intoxication and has been granted Breakthrough Therapy designation by the FDA. A Phase 2 study of TNX-1300 is expected to be initiated in the third quarter of 2023. Tonix's rare disease development portfolio includes TNX-2900 (intranasal potentiated oxytocin) for the treatment of Prader-Willi syndrome. TNX-2900 has been granted Orphan Drug designation by the FDA. Tonix's immunology development portfolio includes biologics to address organ transplant rejection, autoimmunity and cancer, including TNX-1500, which is a humanized monoclonal antibody targeting CD40-ligand (CD40L or CD154) being developed for the prevention of allograft rejection and for the treatment of autoimmune diseases. A Phase 1 study of TNX-1500 is expected to be initiated in the third quarter of 2023. Tonix's infectious disease pipeline includes TNX-801, a vaccine in development to prevent smallpox and mpox. TNX-801 also serves as the live virus vaccine platform or recombinant pox vaccine platform for other infectious diseases. The infectious disease development portfolio also includes TNX-3900 and TNX-4000, classes of broad-spectrum small molecule oral antivirals.

** Tonix's product development candidates are investigational new drugs or biologics and have not been approved for any indication.*

This press release and further information about Tonix can be found at www.tonixpharma.com.

Forward Looking Statements

Certain statements in this press release are forward-looking within the meaning of the Private Securities Litigation Reform Act of 1995. These statements may be identified by the use of forward-looking words such as "anticipate," "believe," "forecast," "estimate," "expect," and "intend," among others. These forward-looking statements are based on Tonix's current expectations and actual results could differ materially. There are a number of factors that could cause actual events to differ materially from those indicated by such forward-looking statements. These factors include, but are not limited to, risks related to the failure to obtain FDA clearances or approvals and noncompliance with FDA regulations; risks related to the failure to successfully market any of our products; risks related to the timing and progress of clinical development of our product candidates; our need for additional financing; uncertainties of patent protection and litigation; uncertainties of government or third party payor reimbursement; limited research and development efforts and dependence upon third parties; and substantial competition. As with any pharmaceutical under development, there are significant risks in the development, regulatory approval and commercialization of new products. Tonix does not undertake an obligation to update or revise any forward-looking statement. Investors should read the risk factors set forth in the Annual Report on Form 10-K for the year ended December 31, 2022, as filed with the Securities and Exchange Commission (the "SEC") on March 13, 2023, and periodic reports filed with the SEC on or after the date thereof. All of Tonix's forward-looking statements are expressly qualified by all such risk factors and other cautionary statements. The information set forth herein speaks only as of the date thereof.

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Zembrace® SymTouch® (sumatriptan Injection): IMPORTANT SAFETY INFORMATION

Zembrace SymTouch (Zembrace) can cause serious side effects, including heart attack and other heart problems, which may lead to death. Stop use and get emergency help if you have any signs of a heart attack:

- discomfort in the center of your chest that lasts for more than a few minutes or goes away and comes back
- severe tightness, pain, pressure, or heaviness in your chest, throat, neck, or jaw
- pain or discomfort in your arms, back, neck, jaw or stomach
- shortness of breath with or without chest discomfort
- breaking out in a cold sweat
- nausea or vomiting
- feeling lightheaded

Zembrace is not for people with risk factors for heart disease (high blood pressure or cholesterol, smoking, overweight, diabetes, family history of heart disease) unless a heart exam shows no problem.

Do not use Zembrace if you have:

- history of heart problems
- narrowing of blood vessels to your legs, arms, stomach, or kidney (peripheral vascular disease)
- uncontrolled high blood pressure

- hemiplegic or basilar migraines. If you are not sure if you have these, ask your provider.
- had a stroke, transient ischemic attacks (TIAs), or problems with blood circulation
- severe liver problems
- taken any of the following medicines in the last 24 hours: almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, ergotamines, dihydroergotamine.
- are taking certain antidepressants, known as monoamine oxidase (MAO)-A inhibitors or it has been 2 weeks or less since you stopped taking a MAO-A inhibitor. Ask your provider for a list of these medicines if you are not sure.
- an allergy to sumatriptan or any of the components of Zembrace

Tell your provider about all of your medical conditions and medicines you take, including vitamins and supplements.

Zembrace can cause dizziness, weakness, or drowsiness. If so, do not drive a car, use machinery, or do anything where you need to be alert.

Zembrace may cause serious side effects including:

- changes in color or sensation in your fingers and toes
- sudden or severe stomach pain, stomach pain after meals, weight loss, nausea or vomiting, constipation or diarrhea, bloody diarrhea, fever
- cramping and pain in your legs or hips; feeling of heaviness or tightness in your leg muscles; burning or aching pain in your feet or toes while resting; numbness, tingling, or weakness in your legs; cold feeling or color changes in one or both legs or feet
- increased blood pressure including a sudden severe increase even if you have no history of high blood pressure
- medication overuse headaches from using migraine medicine for 10 or more days each month. If your headaches get worse, call your provider.
- serotonin syndrome, a rare but serious problem that can happen in people using Zembrace, especially when used with anti-depressant medicines called SSRIs or SNRIs. Call your provider right away if you have: mental changes such as seeing things that are not there (hallucinations), agitation, or coma; fast heartbeat; changes in blood pressure; high body temperature; tight muscles; or trouble walking.
- hives (itchy bumps); swelling of your tongue, mouth, or throat
- seizures even in people who have never had seizures before

The most common side effects of Zembrace include: pain and redness at injection site; tingling or numbness in your fingers or toes; dizziness; warm, hot, burning feeling to your face (flushing); discomfort or stiffness in your neck; feeling weak, drowsy, or tired.

Tell your provider if you have any side effect that bothers you or does not go away. These are not all the possible side effects of Zembrace. For more information, ask your provider.

This is the most important information to know about Zembrace but is not comprehensive. For more information, talk to your provider and read the Patient Information and Instructions for Use. You can also visit www.upsher-smith.com or call 1-888-650-3789.

You are encouraged to report adverse effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

INDICATION AND USAGE

Zembrace is a prescription medicine used to treat acute migraine headaches with or without aura in adults who have been diagnosed with migraine.

Zembrace is not used to prevent migraines. It is not known if it is safe and effective in children under 18 years of age.

Tosymra® (sumatriptan nasal spray): IMPORTANT SAFETY INFORMATION

Tosymra can cause serious side effects, including heart attack and other heart problems, which may lead to death. Stop Tosymra and get emergency medical help if you have any signs of heart attack:

- discomfort in the center of your chest that lasts for more than a few minutes or goes away and comes back
- severe tightness, pain, pressure, or heaviness in your chest, throat, neck, or jaw
- pain or discomfort in your arms, back, neck, jaw, or stomach
- shortness of breath with or without chest discomfort
- breaking out in a cold sweat
- nausea or vomiting
- feeling lightheaded

Tosymra is not for people with risk factors for heart disease (high blood pressure or cholesterol, smoking, overweight, diabetes, family history of heart disease) unless a heart exam is done and shows no problem.

Do not use Tosymra if you have:

- history of heart problems
- narrowing of blood vessels to your legs, arms, stomach, or kidney (peripheral vascular disease)
- uncontrolled high blood pressure
- severe liver problems
- hemiplegic or basilar migraines. If you are not sure if you have these, ask your healthcare provider.
- had a stroke, transient ischemic attacks (TIAs), or problems with blood circulation
- taken any of the following medicines in the last 24 hours: almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, ergotamines, or dihydroergotamine. Ask your provider if you are not sure if your medicine is listed above.

- are taking certain antidepressants, known as monoamine oxidase (MAO)-A inhibitors or it has been 2 weeks or less since you stopped taking a MAO-A inhibitor. Ask your provider for a list of these medicines if you are not sure.
- an allergy to sumatriptan or any ingredient in Tosymra

Tell your provider about all of your medical conditions and medicines you take, including vitamins and supplements.

Tosymra can cause dizziness, weakness, or drowsiness. If so, do not drive a car, use machinery, or do anything where you need to be alert.

Tosymra may cause serious side effects including:

- changes in color or sensation in your fingers and toes
- sudden or severe stomach pain, stomach pain after meals, weight loss, nausea or vomiting, constipation or diarrhea, bloody diarrhea, fever
- cramping and pain in your legs or hips, feeling of heaviness or tightness in your leg muscles, burning or aching pain in your feet or toes while resting, numbness, tingling, or weakness in your legs, cold feeling or color changes in one or both legs or feet
- increased blood pressure including a sudden severe increase even if you have no history of high blood pressure
- medication overuse headaches from using migraine medicine for 10 or more days each month.**If your headaches get worse, call your provider**.
- serotonin syndrome, a rare but serious problem that can happen in people using Tosymra, especially when used with anti-depressant medicines called SSRIs or SNRIs. **Call your provider right away if you have** mental changes such as seeing things that are not there (hallucinations), agitation, or coma; fast heartbeat; changes in blood pressure; high body temperature; tight muscles; or trouble walking.
- hives (itchy bumps); swelling of your tongue, mouth, or throat
- seizures even in people who have never had seizures before

The most common side effects of Tosymra include: tingling, dizziness, feeling warm or hot, burning feeling, feeling of heaviness, feeling of pressure, flushing, feeling of tightness, numbness, application site (nasal) reactions, abnormal taste, and throat irritation.

Tell your provider if you have any side effect that bothers you or does not go away. These are not all the possible side effects of Tosymra. For more information, ask your provider.

This is the most important information to know about Tosymra but is not comprehensive. For more information, talk to your provider and read the Patient Information and Instructions for Use. You can also visit www.upsher-smith.com or call 1-888-650-3789.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

INDICATION AND USAGE
Tosymra is a prescription medicine used to treat acute migraine headaches with or without aura in adults.

Tosymra is not used to treat other types of headaches such as hemiplegic or basilar migraines or cluster headaches.

Tosymra is not used to prevent migraines. It is not known if Tosymra is safe and effective in children under 18 years of age.
