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Tonix Pharmaceuticals Announces Accelerating Completion of Enrollment in Phase 2 UPLIFT Study of TNX-601 ER (Racemic Tianeptine) for Major Depressive Disorder: Topline Data Now Expected in Fourth Quarter 2023

Reallocating Resources to Development of Single Isomer TNX-4300 (Estianeptine)

Estianeptine in Preclinical Development Has Demonstrated Key Activities Related to in vivo Novel Object Recognition and in vitro Neuroplasticity, Without the μ-Opioid Receptor Activity of Racemic and (R)-Tianeptine

New Findings Support Development of TNX-4300 as a First-in-Class Oral Therapyin Depression, Alzheimer's Disease and Other Psychiatric and Neurodegenerative Conditions with Memory Deficits

CHATHAM, N.J., July 26, 2023 (GLOBE NEWSWIRE) -- Tonix Pharmaceuticals Holding Corp. (Nasdaq: TNXP) (Tonix or the Company), a biopharmaceutical company, today announced that development of TNX-4300* (estianeptine), the single *(S)*-isomer of tianeptine will be prioritized over TNX-601 ER*, which is being studied in the Phase 2 UPLIFT[1] trial for the treatment of major depressive disorder (MDD). TNX-4300 is in preclinical development for mood disorders, Alzheimer's disease and Parkinson's disease. Recent findings have shown estianeptine possesses the ability to improve memory and cognition *in vivo* as measured in the rat Novel Object Recognition (NOR) test, and the ability to restore neuroplasticity to neurons in cell culture. The finding that estianeptine is responsible for improving memory and cognition *in vivo* suggests a role for peroxisome proliferator-activated receptor PPAR-β/δ activation in memory. For these reasons, Tonix intends to accelerate completion of enrollment for the Phase 2 UPLIFT[1] trial to reallocate resources to the preclinical development of TNX-4300 and now expects to report topline data from this study in the fourth quarter of 2023. Tonix is also accelerating completion of enrollment in the RESILIENT study of TNX-102 SL for the management of fibromyalgia so that approximately 450 patients will be enrolled, and topline results are expected in the fourth quarter of 2023.

Racemic 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 PPAR-β/δ. 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 also recently reported that estianeptine induces neuroplasticity in cell culture.[2] Together these findings support the development of estianeptine in psychiatric and neurodegenerative diseases."

"Given the time and expense of developing new drugs, the scientific and clinical advantages of TNX-4300 lead us to focus our efforts on this preclinical program as a potential treatment for mood disorders like depression and neurodegenerative conditions like Alzheimer's disease," said Gregory Sullivan, M.D., Chief Medical Officer of Tonix Pharmaceuticals. "The finding that TNX-4300 possesses the desirable attributes of racemic tianeptine and at the same time lacks a measurable opioid liability supports the focus of our resources on this candidate. Multiple studies around the world have already shown that racemic tianeptine is effective in treating depression. However, our *in vivo* animal studies and *in vitro* lab studies have indicated that TNX-4300 is potentially a more active and safer drug."

Dr. Sullivan continued, "TNX-601 ER, which contains racemic tianeptine, has informed the future 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]

Tonix has filed patents claiming single *(S)*-isomer estianeptine, the active ingredient in TNX-4300, which is devoid of activity on the μ-opioid receptor in tissue culture. Tonix has filed patent claims that describe crystalline salt forms of estianeptine that appear well suited to formulation. 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[10] 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.

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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, nearing complete enrollment in a potentially registration-enabling study with topline data expected in the fourth quarter of 2023. TNX-102 SL is also being developed to treat Long COVID, a chronic post-acute COVID-19 condition. Enrollment in a Phase 2 proof-of-concept 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 nearing complete enrollment with topline results of a proof-of-concept study expected in the fourth quarter of 2023. 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, has completed enrollment 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.*

Tonix Medicines has contracted to acquire the Zembrace SymTouch and Tosymra registered trademarks. Intravail is a registered trademark of Aegis Therapeutics, LLC, a wholly owned subsidiary of Neurelis, Inc.

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.

Source: Tonix Pharmaceuticals Holding Corp.