TaiGen Biotechnology

Taigexyn® Nemonoxacin Capsule 250 mg

Read the prescribing information carefully and use under physician's guidance.

WARNING: Quinolones may be associated with physical disorders and potentially irreversible serious adverse reactions, including tendinitis, tendon rupture, peripheral neuritis, and central nervous system effects *[see Warnings and Precautions (4.4)]*.

1. Drug Name
Taigexyn® Nemonoxacin Capsule 250 mg

2. Active Ingredient
Each capsule contains 346 mg of nemonoxacin malate, equivalent to 250 mg of nemonoxacin.

3. Formulation
Light blue capsule (size 0) with "TG" printed in black on one side, and "250" printed in black on the other.

4. Clinical Characteristics

4.1 Indications
Treatment for adults with infections caused by pathogenic bacteria susceptible to nemonoxacin: suitable for out-patients with mild community-acquired pneumonia.

Note: Not recommended for patients ≧ 65 years old due to lack of evidence of efficacy and safety. Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing the infection and to determine their susceptibility to nemonoxacin. Therapy with Taigexyn® may be initiated before the results of these tests are known; once results become available, appropriate therapy should be selected.

4.2 Dosage and Administration

Dosage
Oral administration of 0.5 g (two capsules) once daily for adults on an empty stomach (at least 2 hours before or after meal).

Administration method
Swallow whole capsule with water.

Treatment Duration
Treatment duration should be determined according to the severity of the symptoms or clinical response. The recommended treatment duration is 7 to 10 days.

Special Populations
Geriatric
There is insufficient evidence in efficacy and safety of nemonoxacin for patients ≧ 65 years old.

Pediatric
The efficacy and safety of nemonoxacin in pediatric subjects have not been conducted.

Hepatic Impairment
The efficacy and safety of nemonoxacin in hepatically impaired patients have not been conducted.

Renal Impairment
Nemonoxacin is not recommended for patients with moderate to severe renal impairment, including patients with end-stage renal disease (ESRD). Dose adjustment of mild renal impairment patients [creatinine clearance (CLcr) 60~90 mL/min], are not necessary according to the population pharmacokinetics studies.

4.3 Contraindications
- Patients with known hypersensitivity to any ingredients of this drug or other quinolone antibacterials.
- Pregnant or nursing women.
- Children or teenagers.

4.4 Warnings and Precautions
Avoid use in patients who previously had serious adverse reactions after quinolone or fluoroquinolone use.

According to reports, the following serious adverse events have been observed after administration of other fluoroquinolone antibacterials: tendinopathy and tendon rupture, exacerbation of myasthenia gravis, pseudomembranous colitis, hypersensitivity reactions, photosensitivity/phototoxicity, severe dermatologic reactions, psychiatric reactions, central nervous system effects, peripheral neuropathy, hepatotoxicity, blood glucose disturbances. These serious adverse events were observed in other fluoroquinolone antibacterials.

Nemonoxacin is a new non-fluorinated quinolone. Until September 2013, a total of 1034 subjects had been treated with oral nemonoxacin and the serious adverse events described above were not observed. Nevertheless, attention should be paid to these serious adverse events when nemonoxacin is administered.

Tendinopathy and Tendon Rupture
Tendinitis and tendon rupture (frequently involving the Achilles tendon) can sometimes occur bilaterally, and may occur very quickly within 48 hours or several months after quinolone use. Elderly patients, renal dysfunction, patients who have undergone organ transplantation, or concurrent use of corticosteroids may increase the risk of tendinitis and tendon rupture. Therefore, avoid use of corticosteroids when using Taigexyn®. Tendinitis or tendon rupture has not been reported following Taigexyn® use; however, patients should still be closely monitored. When there are early signs of tendinitis (such as pain, swelling, inflammation), Taigexyn® should be discontinued and alternative drugs should be considered. The affected limb should be treated appropriately (e.g., stabilized). Corticosteroids should be avoided if signs of tendinopathy occur.

Exacerbation of Myasthenia Gravis
According to reports, fluoroquinolones have neuromuscular blocking activity and may exacerbate muscle weakness in persons with myasthenia gravis. No cases of myasthenia gravis exacerbation have been reported following Taigexyn® use; however, patients should still be closely monitored and those with known history of myasthenia gravis should avoid Taigexyn®.

Pseudomembranous Colitis
According to reports, rare cases of pseudomembranous colitis have been observed following administration of broad spectrum antibiotics. No cases of pseudomembranous colitis have been reported following Taigexyn® use; however, patients should still be closely monitored. If the patient develops severe diarrhea, relationship to Taigexyn® should be considered. Taigexyn® should be discontinued immediately if pseudomembranous colitis is suspected or confirmed, and appropriate treatment for the patient should be provided.

Hypersensitivity Reactions
According to reports, rare cases of serious or occasionally fatal hypersensitivity reactions (e.g. angioedema that leads to anaphylactic shock) have been observed after using other fluoroquinolone antibacterials, some cases occurred after the first dose. No cases have been reported following Taigexyn® use; however, patients still need to be closely monitored and drug therapy should be discontinued immediately if serious hypersensitivity reactions are observed. The patient's healthcare provider should be contacted or appropriate medical care should be provided at the emergency room.

Photosensitivity/Phototoxicity
According to reports, rare cases of moderate to severe photosensitivity/phototoxicity reactions after sun or UV light exposure, associated to the administration of other fluoroquinolone drugs, have been observed. These present as excessive sun exposure responses of the exposed body parts (e.g., burning, erythema, exudation, vesicles, blistering, edema). No cases have been reported following Taigexyn® use; however, patients still need to be closely monitored and excessive exposure to these sources of light should be avoided. Drug therapy should be discontinued if photosensitivity/phototoxicity occurs.

Severe Blistering Reactions
According to reports, rare cases of moderate to severe blistering reactions such as Stevens-Johnson syndrome or toxic epidermal necrolysis have been observed after use of other fluoroquinolone antibacterials. No cases have been reported following Taigexyn® use; however, patients still need to be closely monitored. It is suggested that patients showing skin and/or mucosal reactions should inform their healthcare provider immediately to determine if the drug should be continued.

Psychiatric reactions
According to reports, rare cases of psychiatric reactions have been observed after use of other fluoroquinolone antibacterials. In extremely rare cases, these psychiatric reactions developed into suicidal thoughts and acts. No cases have been reported following Taigexyn® use; however, patients still need to be closely monitored, and drug therapy should be discontinued and appropriate measures instituted if patient developed such reactions. Drug therapy should be used with caution, especially in patients with psychiatric disorder or a history of psychiatric disorder.

Central Nervous System Effects
(1) Psychiatric-related adverse reactions: Quinolone drugs may increase psychiatric-related adverse effects, including toxic psychosis, psychotic reactions developing into suicidal thoughts/ideas, hallucinations or delusions; depression or self-harming behavior such as attempted suicide or completion of suicide; anxiety, agitation or nervousness; mental confusion, timidity, loss of direction or loss of concentration; insomnia or nightmares; impaired memory. These reactions may occur after the first dose. No cases have been reported following Taigexyn® use; however, patients still need to be closely monitored. If any of the above reactions are observed, medical staff should be informed immediately, drug therapy should be discontinued, and appropriate treatment should be provided to the patient.

(2) Central nervous system adverse reactions: Quinolone drugs may be associated with increased risk of epilepsy (spasm), increased intracranial pressure (pseudotumor cerebri), dizziness, and tremor. These kinds of drugs are known to induce epilepsy or reduce the threshold of epilepsy. Cases of epileptic seizures had been reported. Caution should be taken when use in patients with epilepsy and known or suspected central nervous system disorders that may induce epilepsy or reduce the threshold of epilepsy (e.g., severe cerebral arteriosclerosis, history of spasms, decreased blood flow to the brain, structural changes in the brain, or stroke), or other patients who have risk factors that could induce epilepsy or reduce the threshold of epilepsy (such as drugs, renal insufficiency). In the event of epilepsy, the drug should be discontinued and appropriate therapy should be initiated.

Peripheral Neuropathy
According to reports, cases of sensory or sensorimotor axonal neuropathy have been observed after using other fluoroquinolone antibacterials. Symptoms may occur soon after drug administration. No cases have been reported following Taigexyn® use; however, patients still need to be closely monitored. Drug therapy should be discontinued if the patient experiences symptoms of neuropathy in order to avoid development of irreversible conditions.

Hepatotoxicity
According to reports, rare cases of liver necrosis or even fatal liver failure have been observed after using other fluoroquinolone antibacterials. Most of these cases occurred in patients with potentially severe disease such as septicemia. In a comparative analysis of integrated phase II/III studies, neither the Taigexyn® nor the levofloxacin control group showed increased ALT (GPT) 3 times higher than normal range. But, the proportion of subjects with increased AST (GOT) 3 times higher than normal range was 1.3% in the Taigexyn® 500 mg group and 0.4% in the levofloxacin control group. No hepatotoxicity has been reported following Taigexyn® use; however, patients still need to be closely monitored. Patients should be advised to discontinue treatment and contact their healthcare provider if they develop signs and symptoms of liver disease such as loss of appetite, jaundice, dark urine, abdominal itching or tenderness.

Blood Glucose Metabolism Disorders
Quinolone drugs may be associated with disturbances of blood glucose, including symptomatic hyperglycemia and hypoglycemia, which usually occurs in diabetic patients receiving concomitant treatment with an oral hypoglycemic agent (such as glyburide) or with insulin. In these patients, careful monitoring of blood glucose is recommended. There have been reported cases of severe hypoglycemia leading to coma or death. No symptomatic hyperglycemia or hypoglycemia (e.g., diabetic coma) have been reported following Taigexyn® use; however, blood glucose level of diabetic patients during drug therapy should be carefully monitored. If a hypoglycemic reaction occurs in a patient being treated with Taigexyn®, Taigexyn® should be discontinued and appropriate therapy should be initiated immediately.

QT Prolongation
A total of 48 healthy adult subjects showed positive results during a thorough QT study, indicating that nemonoxacin poses a risk of electrocardiogram (ECG) QTc prolongation. The thorough QT study showed that the therapeutic dose of 500 mg Taigexyn® induced shorter QTc prolongation when compared with control drug moxifloxacin 400 mg; maximum mean change of QTc interval was by 8.74 millisecond (Taigexyn®) and 13.04 millisecond (control drug). Drug use should be avoided in patients with known prolongation of the QT interval, patients with uncorrected hypokalemia, and patients receiving class Ia (e.g. quinidine, procainamide) or class III (e.g. amiodarone, sotalol) anti-arrhythmic medications. Taigexyn® may have cumulative effects when co-administered with other drugs that may prolong QT interval, such as erythromycin, antipsychotics, and tricyclic antidepressants. Therefore, these concomitant medications should be used with caution. Drug should be used with caution in the presence of factors that may cause arrhythmia, such as severe bradycardia or acute myocardial ischemia. Female and elderly patients might be more susceptible to drug-associated effects on the QT interval. QT interval prolongation may cause ventricular arrhythmia (including torsades de pointes).

4.5 Drug Interactions
According to results of *in vitro* tests at clinical concentrations, nemonoxacin has neither any significant inhibitory effects on CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 or 3A4 nor any significant inducing effects on CYP1A2, 2B6, 2C8, 2C9, 2C19 or 3A4. *In vitro* study on the effect of nemonoxacin on UGT2B7 has not been completed. *In vitro* studies showed that nemonoxacin is the substrate of P-glycoprotein (P-gp).

Probenecid
A study of 12 healthy subjects who took probenecid (single oral dose of 0.5 g, total 1.5 g) orally 1 hour before, 12 hours after, and 24 hours after administration of Taigexyn® (single oral dose of 500 mg) showed a reduction in renal clearance of nemonoxacin by 23.7%; $AUC_{0\text{-}inf}$ was increased by 25.4%. Taigexyn® should be used with caution when combined with probenecid and patients should be closely monitored.

Aluminum-Magnesium Preparations
A study of 12 healthy subjects who took Taigexyn® (single oral dose of 500 mg) with aluminum-magnesium preparations (single oral dose of 0.918 g aluminum hydroxide and 1.2 g magnesium hydroxide) showed a significant reduction in exposure to nemonoxacin ($AUC_{0\text{-}inf}$ reduced by approximately 81.1%, C_{max} reduced by approximately 78.7%); taking Taigexyn® 4 hours after administration of aluminum-magnesium preparations also showed a significant reduction in exposure to nemonoxacin ($AUC_{0\text{-}inf}$ reduced by approximately 74.3%, C_{max} reduced by approximately 80.5%) . However, taking aluminum-magnesium preparations 2 hours after Taigexyn® did not significantly change nemonoxacin exposure ($AUC_{0\text{-}inf}$ reduced by approximately 8.9%). Antacids or other "preparations containing aluminum and/or magnesium ions" must be taken 2 hours after taking Taigexyn® if concomitant medication is needed. In addition, sucralfate should also be taken at least 2 hours after administration of Taigexyn®.

Ferrous Sulfate
A study of 12 healthy subjects who took Taigexyn® (single oral dose of 500 mg) with ferrous sulfate (single oral dose of 0.3 g) showed a significant reduction in exposure to nemonoxacin ($AUC_{0\text{-}inf}$ reduced by approximately 63.9%, C_{max} reduced by approximately 60.9%). Combination of Taigexyn® with preparation containing ferric or ferrous ions (e.g. ferrous sulfate) should be avoided. If preparation containing ferric or ferrous ions is decided to be used after a risk-benefit assessment, it should be used at least 2 hours after administration of Taigexyn®.

Calcium Carbonate
A study of 12 healthy subjects who took Taigexyn® (single oral administration of 500 mg) with calcium carbonate (single oral administration of 1.5 g) showed a reduction in exposure to nemonoxacin ($AUC_{0\text{-}inf}$ reduced by approximately 18.8%, C_{max} reduced by approximately 16.2%). Due to the small reduction in exposure, when Taigexyn® needs to be used in combination with preparations containing calcium ions (e.g. calcium carbonate) dosage of Taigexyn® need not be adjusted. However, multivitamins containing zinc or other metal cations should be used at least 2 hours after administration of Taigexyn®.

Theophylline
A study of 11 healthy subjects who took Taigexyn® (daily oral administration of 500 mg for 5 consecutive days) with theophylline (oral administration of 0.2 g, once a day on Days 1 and 5; oral administration of 0.2 g twice a day on Days 2, 3, and 4) showed multiple-dose nemonoxacin exposure was not significantly changed during its steady state; theophylline exposure was slightly increased ($AUC_{0\text{-}inf}$ increased by approximately 16.7%, C_{max} increased by approximately 15.2%). Taigexyn® should be used with caution when co–administered with theophylline, with close monitoring of the blood levels of theophylline and proper dose adjustment.

Warfarin
A study of 16 healthy subjects who took Taigexyn® continuously (daily oral administration of 500 mg for 8 consecutive days) and co-administered warfarin on Day 4 (single oral administration of 5 mg) showed patients' R-warfarin and S-warfarin exposures were not significantly changed due to administration of Taigexyn® . The prothrombin time did not change significantly either. However, according to reports, the use of other fluoroquinolone antibacterials may increase patients' anticoagulant effect of warfarin. Therefore, coagulation parameters (PT, INR or other coagulation tests) should be closely monitored when Taigexyn® is co-administered with warfarin or its derivatives.

Cimetidine
A study of 11 healthy subjects who took Taigexyn® (oral administration of 500 mg on Day 5) and cimetidine (oral administration of 400 mg 3 times per day for 7 consecutive days) showed no significant changes in nemonoxacin exposure. No dose adjustment is necessary when Taigexyn® is used with cimetidine.

Non-steroidal anti-inflammatory drugs
According to reports, combination of non-steroidal anti-inflammatory drugs and fluoroquinolone drugs may increase the risk of CNS stimulation and convulsive seizures. Adverse reactions related to central nervous system should be monitored when Taigexyn® is combined with non-steroidal anti-inflammatory drugs.

Antidiabetic Agents
According to reports, combination of antidiabetic agents and fluoroquinolone antibacterials has been reported to cause symptomatic hyperglycemic or hypoglycemic reactions (e.g. glycemic coma). Blood sugar levels need to be carefully monitored when Taigexyn® is combined with antidiabetic agents and drug therapy should be discontinued immediately with appropriate treatment once symptomatic hyperglycemic or hypoglycemic reactions are observed.

4.6 Use by Pregnant or Nursing Mothers
Pregnancy
Safety of Taigexyn® in pregnant women is not yet determined and cannot be assured. Therefore, Taigexyn® is prohibited in pregnant or potentially pregnant women.

Nursing Mothers
Safety of Taigexyn® in nursing mothers not yet studied and cannot be assured. Therefore, Taigexyn® is prohibited in nursing mothers. Taigexyn® can only be given to nursing mothers when the potential benefit justifies the potential risk to nursing mother, but breastfeeding should be put on hold.

4.7 Pediatric Use
Efficacy and safety of Taigexyn® in pediatric subjects have not been conducted.

4.8 Geriatric Use
There is inadequate evidence of efficacy and safety for Taigexyn® in patients who are 65 years of age or older. Therefore, it is not recommended.

4.9 Adverse Reactions
The safety profile of nemonoxacin was established using the safety population of oral nemonoxacin, which includes 1381 subjects. As of March 31, 2013, the safety results of two phase II clinical studies and one phase III clinical study in patients with community-acquired pneumonia were integrated to become an integrated phase II/III comparative population. This integrated population included 987 subjects, of which 670 (67.88%) received oral nemonoxacin [519 patients (52.58%) received nemonoxacin 500 mg and 151 (15.30%) received nemonoxacin 750 mg], while 317 (32.12%) received levofloxacin500 mg. The incidences of drug-related adverse events occurring in ≥1% of patients receiving nemonoxacin 500 mg daily (integrated phase II/III comparative population) are shown in the table below.

Frequency	Common (≥ 1%)
Gastrointestinal disorders	Nausea 2.5% Diarrhea 1.3% Vomiting 1.2% Abdominal discomfort 1.0%
Blood and lymphatic system disorders	Neutropenia 1.9%
Nervous system disorders	Dizziness 1.9% Headache 1.0%
Investigations	ALT (SGPT) increased 4.4% White blood cell count decreased 2.1% AST (SGOT) increased 1.9% GGT increased 1.3%

In patients with community-acquired pneumonia who received 500 mg nemonoxacin, the following incidence rates were relatively higher: ALT (SGPT) increased (4.4%), nausea (2.5%), white blood cell count decreased (2.1%), neutropenia (1.9%), dizziness (1.9%), and AST (SGOT) increased (1.9%). The increase in liver enzymes (ALT/AST) was temporary, and none of the patients met the Hy's law of drug-induced liver injury (DILI).

4.10 Overdosage
There is limited study information regarding drug overdose. The maximum single oral dose in healthy adults was 1.5 g. No significant adverse reactions were observed after taking nemonoxacin for 10 consecutive days at a maximum daily dose of 1 g. In the event of an overdose, patients should be treated according to their conditions. Electrocardiogram tests should be performed since there is a risk of QT interval prolongation.

5. Pharmacological Properties

5.1 Pharmacodynamic Properties
Mechanism of Action
Nemonoxacin is a non-fluorinated quinolone antibiotic. Nemonoxacin was effective against a wide variety of gram-negative and gram-positive bacteria in *in vitro* studies. Nemonoxacin exerts its effect by inhibition of DNA gyrase and topoisomerase IV, and thus inhibits the synthesis of DNA, which is necessary for bacterial growth. *Streptococcus pneumoniae* with mutations in DNA gyrase and topoisomerase (double mutations) is resistant to most fluorinated quinolones. *In vitro* tests showed that nemonoxacin can treat *Streptococcus pneumoniae* infection at an appropriate concentration that inhibits the two enzyme systems. In addition, the minimum inhibitory concentration of nemonoxacin against bacterial strains with double mutations is still within the range of effective concentrations required to inhibit the growth of common bacteria.

Drug Resistance
The primary mechanisms of resistance to fluorinated quinolones are mutations in DNA gyrase and/or topoisomerase IV. The mechanisms underlying the resistance of bacteria to nemonoxacin are similar to that of fluorinated quinolones which involves multiple steps of mutation and efflux pump. The frequency of spontaneous mutation is low ($< 10^{-10}$ to 10^{-6}). However, the site of action of nemonoxacin is different from that of fluorinated quinolones. For new non-fluorinated quinolones such as nemonoxacin, cross-resistance was not observed between nemonoxacin and fluorinated quinolones from current limited data. Further observations in the clinical setting are required to determine if cross-resistance will occur.

The mechanism of action is different for quinolones (including nemonoxacin) and macrolides, β-lactams, aminoglycosides, and tetracyclines; therefore, the microorganisms resistant to drugs belonging to these classes of antibiotics may be susceptible to nemonoxacin and other quinolones. There is no known cross-resistance between nemonoxacin and the classes of antibiotics mentioned above. Nemonoxacin is effective against macrolide- and penicillin-resistant strains *in vitro*.

Antibacterial Spectrum of Activity
Nemonoxacin has been shown to be active against the isolates of the following bacteria both *in vitro* and in clinical studies *[see Clinical Studies (5.4)]*.

Gram-positive bacteria
Streptococcus pneumoniae (including penicillin-susceptible[1], -intermediate and -resistant *Streptococcus pneumoniae*)
Staphylococcus aureus (including methicillin-susceptible[1] and -resistant *Staphylococcus aureus*)

Gram-negative bacteria
Haemophilus influenzae[1]
Haemophilus parainfluenzae[1]
Klebsiella pneumoniae[1]
Escherichia coli
Moraxella catarrhalis

Atypical strains[2]
Mycoplasma pneumoniae[1]
Chlamydia pneumoniae[1]
Legionella pneumophila[1]

Nemonoxacin has been shown to be active against the following isolates (≥ 90%) at MICs of ≤ 0.5 mg/L (against gram-positive, aerobic bacteria) and ≤ 2.0 mg/L (against gram-negative, aerobic bacteria) *in vitro*; however, currently, there are no adequate and well-controlled clinical studies to prove the efficacy and safety of nemonoxacin in treating infections caused by these microorganisms.

Gram-positive bacteria
Streptococcus pyogenes

Gram-negative bacteria
Klebsiella oxytoca[3]

Note: The above listed antibacterial spectrums of activity not marked with 1 are results of *in vitro* tests. Clinical results on susceptible isolated strains are supported by clinical trial data. Data of antibacterial spectrum of activity for Taiwan strains are not available. Currently only supported by limited isolated strains from USA or China. Data of Taiwan strains are not available.

5.2 Pharmacokinetic Properties
Absorption
Nemonoxacin is rapidly and completely absorbed after oral administration under fasted condition. Peak plasma concentrations are usually attained within 1 to 2 hours after oral dosing. Pharmacokinetic linearity and/or dose proportionality are approximately statistically achieved over the doses from 75 to 1,000 mg evaluated. Following a once-daily oral dose of nemonoxacin 500 mg for 10 consecutive days, the mean peak plasma concentration (C_{max}) and systemic exposure ($AUC_{0\text{-}24h}$) were 7.02 μg/mL and 46.9 μg·h/mL, respectively. Furthermore, the mean accumulation ratio was less than 10% under the fasted condition at steady state. It appeared that the steady state was reached on the third to fifth day following a once-daily oral dose of nemonoxacin 500 mg.
The food-effect study of 500 mg nemonoxacin, means of C_{max} and $AUC_{0\text{-}inf}$ were reduced approximately 36% and 24%, respectively; T_{max} was prolong by approximately 3.5 hours under the high-fat meal condition.

Distribution
In vitro plasma protein binding assay, nemonoxacin is approximately 44% to 48% bound to plasma protein. The mean apparent volume of distribution of nemonoxacin is approximately 107.6 L following 10 consecutive days of a once-daily oral administartion of nemonoxacin 500 mg.

Metabolism
Nemonoxacin is very stable in plasma and urine. Nemonoxacin undergoes limited metabolism in humans and primarily excreted as unchanged drug in urine. Only trace amounts of nemonoxacin acyl-β-D-glucuronide (phase II metabolite) can be detected in urine after oral administration.

Excretion
Nemonoxacin is excreted largely as unchanged drug in urine after oral administration. In healthy subjects, 72.37% of nemonoxacin is excreted as unchanged drug in the urine and 6.11% in the feces. In addition, less than 2% dose is excreted as nemonoxacin acyl-β-D-glucuronide (phase II metabolite) in urine. The mean terminal plasma elimination half-life of nemonoxacin is approximately 12.1 hours.

Specific Populations
Pediatrics
The pharmacokinetics of nemonoxacin in pediatrics subjects has not been conducted.

Age
There are no significant differences in nemonoxacin pharmacokinetics between young and elderly subjects, 18 to 70 years, according to population pharmacokinetic studies.

Gender
Following 10 consecutive days of once-daily oral dose of Taigexyn® 500 mg, $AUC_{0\text{-}24h,ss}$ and $C_{max,ss}$ in female healthy volunteers were higher than male healthy volunteers by 16.5% and 26.4%, respectively. But according results of population pharmacokinetic studies, the total cleanance (CL_T) and mean terminal half-life of female patients was only decreased about 11% and extended about 0.3 hours than male patients, respectively. This difference was attributable to the variation in renal function status of male and female patients and was not believed to be clinical significant. Dose adjustment based on gender alone is not necessary for Taigexyn®.

Hepatic impairment
Pharmacokinetic studies have not been conducted in patients with hepatic impairment.

Renal impairment
Pharmacokinetic studies have not been conducted in patients with renal impairment. Based on population pharmacokinetic studies, systemic exposure at steady state ($AUC_{0\text{-}24h,ss}$ and $C_{max,ss}$) of mild renal impairment patients (CLcr = 60 to 90 mL/min) were increased when compared to patients with normal kidney function, but those values increased by less than 20%. Dose adjustment based on mild renal impairment patients are not necessary for Taigexyn®.

5.3 Preclinical Safety Information
Toxicities produced by nemonoxacin are similar to those of other approved fluoroquinolone antibacterials in the market. *In vitro* safety pharmacology tests showed possible QTc prolongation with nemonoxacin in man. *In vivo* tests showed side effects on the central nervous system and gastrointestinal tract with high doses, such as decreases of spontaneous motor activity and gastric mobility, but no effects were noted on the cardiovascular or respiratory systems. Repeated oral dose toxicity studies of nemonoxacin showed QTc prolongation in monkeys and pathological changes in articular cartilage of juvenile dogs, all of which are known side effects of quinolone antibacterials that were reversible following drug withdrawal. *In vitro* genotoxicity tests showed positive results, whereas *in vivo* tests showed negative results. Animal tests showed that unlike other fluoroquinolone antibacterial, nemonoxacin exhibited neither phototoxicity nor systemic hypersensitive reactions.

Carcinogenesis and Mutagenesis
Carcinogenicity study has not been performed. *In vitro* bacterial reverse-mutation assay (Ames test), chromosome aberration tests on Chinese hamster ovary cells, and mutagenesis studies on $TK^{+/-}$ gene of mouse lymphoma L5178Y cells, all showed positive results. These results are consistent with those of other fluoroquinolone antibacterials. Results of *in vivo* micronucleus test in mouse and *in vivo* unscheduled DNA synthesis test in rats were negative.

Phototoxicity
Nemonoxacin was negative for phototoxicity *in vitro* in mouse fibroblasts (Balb/c 3T3) and in repeated oral dose study for 10 consecutive days in Crl:SKH1-hr hairless mice.

ECG
50 mg/kg nemonoxacin had no significant influence on QT (QTc) interval of ECG in an *in vivo* safety pharmacology test with telemetry ECG monitoring in dogs. Monkeys were orally given 300 mg/kg nemonoxacin in a 28-day repeated dose toxicity test. QTc prolongation and reduced heart rate were observed three hours after administration (on Day 5 and Day 26), but these changes reversed in the next 24 hours.

Development and Reproductive Toxicity
In embryonic development studies in rats and rabbits, the no observed adverse effect level (NOAEL) of embryonic development was 30 and 20 mg/kg/day, respectively; high dose nemonoxacin caused decreased maternal/fetal weight and delayed ossification development. Fertility and early embryonic development studies in rats showed that 1,000 mg/kg nemonoxacin has no significant influence on parental fertility, reproductive parameters, or early embryonic development. However, 600 mg/kg/day oral dose caused a slight decrease in post-natal survival rate of fetus; however, the development and reproductive capacities of the offspring were not affected after weaning. Pregnancy category is C.

Bone/Cartilage and Tendon Toxicity
It was known that quinolone antibacterials can cause pathological changes in cartilage on weight-bearing joints of juvenile animals. This phenomenon was also observed in young dogs given 40 mg/kg/day nemonoxacin for 28 consecutive days, but was not present after 13 weeks post drug withdrawal. NOAEL of nemonoxacin on articular cartilage toxicity of juvenile dogs is 20 mg/kg/day.

Active Systemic Anaphylaxis Test
Guinea pigs were given a total of 5 doses of 10 or 20 mg/kg nemonoxacin by intraperitoneal injection once every other day for induction. Twice the amount of sensitizing dose was injected via the tail vein on Day 10 after the last dose and no hypersensitive reactions were observed.

5.4 Clinical Trials
Community-Acquired Pneumonia
To date, three clinical trials have evaluated the efficacy and safety of nemonoxacin in patients with community-acquired pneumonia, including one phase III pivotal study and two phase II studies.

The primary endpoint of these 3 clinical studies was to determine non-inferiority of nemonoxacin 500 mg to levofloxacin 500 mg at Visit 4 (7 to 14 days after end of therapy).

Analytical results of the primary endpoint from these 3 clinical studies are listed in Table 1. The integrated clinical efficiency of nemonoxacin 500 mg group and levofloxacin 500 mg group in the primary analysis population were 88.7% and 86.4%, respectively.

Statistical analysis results of phase III (TG-873870-C-4) and phase II (TG-873870-C-3) clinical trials showed that the clinical efficacy of nemonoxacin 500 mg in treating community-acquired pneumonia was significantly non-inferior to levofloxacin 500 mg. Oral administration of nemonoxacin 500 mg for 7 to 10 days when compared to oral administration of levofloxacin 500 mg for 7 to 10 days, had similar clinical efficacy.

	Nemonoxacin 500 mg		Levofloxacin 500 mg		% Difference (95% CI)
	n/N	%	n/N	%	
TG-873870-C-4 study	300/328	91.5	143/160	89.4	2.1 (−3.6, 7.7)
TG-873870-C-3 study	56/60	93.3	46/52	88.5	4.9 (−5.9, 15.6)
TG-873870-02 study	67/89	75.3	72/90	80.0	−4.7 (−16.9, 7.5)
Total	423/477	88.7	261/302	86.4	–

%: Denominator of the percentage calculation is the total number of subjects with clinical cure, clinical failure, and subjects who were not evaluable. Clinical cure = 100 × number of subjects with clinical cure/ (number of subjects with clinical cure + number of subjects with clinical failure + subjects who were not evaluable).

Analysis of baseline pathogens demonstrated that nemonoxacin achieved good clinical cure rates (87% to 100%), microbiological success rates (87% to 100%), and overall cure rates (87% to 100%) against common causative pathogens found in community-acquired pneumonia, including penicillin-susceptible *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, and *Klebsiella pneumoniae*. Furthermore, nemonoxacin showed good clinical cure rates (88.2% to 90.5%) against atypical pathogens found in community-acquired pneumonia, e.g., *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella pneumophila*.

6. Pharmaceutical Properties
6.1 Excipients and Capsule Shell Composition
Excipients: microcrystalline cellulose, magnesium stearate. Composition of capsule shell: #0 capsule shell, cap/body composition: gelatin, brilliant blue FCF (E133), erythrosine (E127), titanium dioxide (E171), sodium lauryl sulfate.

6.2 Storage
Taigexyn® must be stored in a dry place, at temperatures not exceeding 25°C; Taigexyn® must be kept in containers provided by the original manufacturer; Taigexyn® must be kept out of reach of children.

6.3 Package
4 to 1000 capsules, plastic bottle or aluminum blister pack.

15 Jan 2020

[Manufacturer] Lotus Pharmaceutical Co., Ltd.

[Manufacturer address] No. 30, Chenggong 1st Road, Nantou City, Nantou County, Taiwan

[Manufacturer] China Chemical & Pharmaceutical Co., Ltd., Hsinfong Plant

[Manufacturer address] No. 182-1, Keng Tze Kou, Hsinfong Shiang, Hsinchu County, Taiwan

[Pharmaceutical company] TaiGen Biotechnology Co., Ltd.

[Company address] 7F, 138 Shin Ming Road, Neihu District, Taipei, Taiwan

[Company phone number] 02-8177-7020