CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209080Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TIGLUTIK™ safely and effectively. See full prescribing information for TIGLUTIK.

TIGLUTIK (riluzole) oral suspension
Initial U.S. Approval: 1995

INDICATIONS AND USAGE

TIGLUTIK is indicated for the treatment of amyotrophic lateral sclerosis (ALS) (1)

DOSAGE AND ADMINISTRATION

- Recommended dosage: 50 mg (10 mL), twice daily, taken orally, every 12 hours (2)
- Take at least 1 hour before or 2 hours after a meal (2)
- Measure serum aminotransferases before and during treatment (2, 5.1)

DOSAGE FORMS AND STRENGTHS

Oral suspension: 50 mg/10 mL (5 mg/mL) in 300 mL multiple-dose bottle (3)

CONTRAINDICATIONS

Patients with a history of severe hypersensitivity reactions to riluzole or to any of its components (4)

WARNINGS AND PRECAUTIONS

- Hepatic injury: Use of TIGLUTIK is not recommended in patients with baseline elevations of serum aminotransferases greater than 5 times the upper limit of normal; discontinue TIGLUTIK if there is evidence of liver dysfunction (5 1)
- Neutropenia: Advise patients to report any febrile illness (5.2)
- Interstitial lung disease: Discontinue TIGLUTIK if interstitial lung disease develops (5.3)

ADVERSE REACTIONS

Most common adverse reactions (incidence greater than or equal to 5% and greater than placebo) were oral hypoesthesia, asthenia, nausea, decreased lung function, hypertension, and abdominal pain (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact ITF Pharma Inc. at 1-800-664-1490 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Strong to moderate CYP1A2 inhibitors: Co-administration may increase TIGLUTIK-associated adverse reactions (7.1)
- Strong to moderate CYP1A2 inducers: Co-administration may result in decreased efficacy (7.2)
- Hepatotoxic drugs: TIGLUTIK-treated patients that take other hepatotoxic drugs may be at increased risk for hepatotoxicity (7.3)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm (8 1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 9/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

TIGLUTIK is indicated for the treatment of amyotrophic lateral sclerosis (ALS).

2 DOSAGE AND ADMINISTRATION

The recommended dosage for TIGLUTIK is 50 mg (10 mL) taken orally twice daily, every 12 hours. TIGLUTIK should be taken at least 1 hour before or 2 hours after a meal *[see Clinical Pharmacology (12.3)]*.

Gently shake the TIGLUTIK bottle for at least 30 seconds before administration (see Instructions for Use for further details).

Measure serum aminotransferases before and during treatment with TIGLUTIK *[see Warnings and Precautions (5.1)]*.

3 DOSAGE FORMS AND STRENGTHS

Oral suspension: 50 mg/10 mL (5 mg/mL) slightly brown, opaque, homogeneous suspension in a 300 mL multiple-dose amber bottle.

4 CONTRAINDICATIONS

TIGLUTIK is contraindicated in patients with a history of severe hypersensitivity reactions to riluzole or to any of its components (anaphylaxis has occurred) *[see Adverse Reactions (6.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hepatic Injury

TIGLUTIK can cause liver injury. Cases of drug-induced liver injury, some of which were fatal, have been reported in patients taking riluzole. Asymptomatic elevations of hepatic transaminases have also been reported, and in some patients have recurred upon re-challenge with riluzole.

In clinical studies, the incidence of elevations in hepatic transaminases was greater in riluzole-treated patients than placebo-treated patients. The incidence of elevations of ALT above 5 times the upper limit of normal (ULN) was 2% in riluzole-treated patients. Maximum increases in ALT occurred within 3 months after starting riluzole. About 50% and 8% of riluzole-treated patients in pooled controlled efficacy studies (Studies 1 and 2) had at least one elevated ALT level above ULN and above 3 times ULN, respectively *[see Clinical Studies (14)]*.

Monitor patients for signs and symptoms of hepatic injury, every month for the first 3 months of treatment, and periodically thereafter. The use of TIGLUTIK is not recommended if patients develop hepatic transaminases levels greater than 5 times the ULN. Discontinue TIGLUTIK if there is evidence of liver dysfunction (e.g., elevated bilirubin). Concomitant use with other hepatotoxic drugs may increase the risk for hepatotoxicity *[see Drug Interactions (7.3)]*.

5.2 Neutropenia

TIGLUTIK can cause neutropenia. Cases of severe neutropenia (absolute neutrophil count less than 500 per mm^3) within the first 2 months of riluzole treatment have been reported. Advise patients to report febrile illnesses.

5.3 Interstitial Lung Disease

TIGLUTIK can cause interstitial lung disease, including hypersensitivity pneumonitis. Discontinue TIGLUTIK immediately if interstitial lung disease develops.

6 ADVERSE REACTIONS

The following adverse reactions are described below and elsewhere in the labeling:

- Hepatic Injury *[see Warnings and Precautions (5.1)]*
- Neutropenia *[see Warnings and Precautions (5.2)]*
- Interstitial Lung Disease *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse Reactions in Controlled Clinical Trials of Riluzole Tablets

In the placebo-controlled clinical trials in patients with ALS (Study 1 and 2), a total of 313 patients received riluzole 50 mg twice daily *[see Clinical Studies (14)]*. The most common adverse reactions in riluzole-treated patients (in at least 5% of patients and more frequently than on placebo) were asthenia, nausea, decreased lung function, hypertension, and abdominal pain. The most common adverse reactions leading to discontinuation in the riluzole group were nausea, abdominal pain, constipation, and elevated ALT.

There was no difference in the rate of adverse reactions leading to discontinuation between females and males. However, the incidence of dizziness was higher in females (11%) than in males (4%). The adverse reaction profile was similar in older and younger patients. There are insufficient data to assess racial differences in the adverse reaction profile.

Table 1 lists adverse reactions that occurred in at least 2% of riluzole-treated patients (50 mg twice daily) in pooled Study 1 and 2, and at a higher rate than on placebo.

Table 1. Adverse Reactions in Pooled Placebo-Controlled Trials (Studies 1 and 2) in Patients with ALS

	Riluzole Tablets 50 mg twice daily (N=313)	Placebo (N=320)
Asthenia	19%	12%
Nausea	16%	11%
Decreased lung function	10%	9%
Hypertension	5%	4%
Abdominal pain	5%	4%
Vomiting	4%	2%
Arthralgia	4%	3%
Dizziness	4%	3%
Dry mouth	4%	3%
Insomnia	4%	3%
Pruritus	4%	3%
Tachycardia	3%	1%
Flatulence	3%	2%
Increased cough	3%	2%
Peripheral edema	3%	2%
Urinary Tract Infection	3%	2%
Circumoral paresthesia	2%	0%
Somnolence	2%	1%
Vertigo	2%	1%
Eczema	2%	1%

Additional Adverse Reactions with TIGLUTIK

In an open-label pharmacokinetic study in healthy subjects (n=36), oral hypoesthesia was observed in 29% of subjects taking TIGLUTIK, compared to 6% in patients taking riluzole tablets, under fasting conditions.

6.2 Postmarketing Experience

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

- Acute hepatitis and icteric toxic hepatitis *[see Warnings and Precautions (5.1)]*
- Renal tubular impairment

7 DRUG INTERACTIONS

7.1 Agents that may Increase Riluzole Blood Concentrations

CYP1A2 Inhibitors

Co-administration of riluzole (a CYP1A substrate) with CYP1A2 inhibitors was not evaluated in a clinical trial; however, in vitro findings suggest an increase in riluzole exposure is likely. The concomitant use of strong or moderate CYP1A2 inhibitors (e.g., ciprofloxacin, enoxacin, fluvoxamine, methoxsalen, mexiletine, oral contraceptives, thiabendazole, vemurafenib, zileuton) with TIGLUTIK may increase the risk of TIGLUTIK - associated adverse reactions *[see Clinical Pharmacology (12.3)]*.

7.2 Agents that may Decrease Riluzole Plasma Concentrations

CYP1A2 Inducers

Co-administration of riluzole (a CYP1A substrate) with CYP1A2 inducers was not evaluated in a clinical trial; however, in vitro findings suggest a decrease in riluzole exposure is likely. Lower exposures may result in decreased efficacy *[see Clinical Pharmacology (12.3)]*.

7.3 Hepatotoxic Drugs

Clinical trials in ALS patients excluded patients on concomitant medications which were potentially hepatotoxic (e.g., allopurinol, methyldopa, sulfasalazine). TIGLUTIK-treated patients who take other hepatotoxic drugs may be at an increased risk for hepatotoxicity *[see Warnings and Precautions (5.1)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no studies of riluzole in pregnant women, and case reports have been inadequate to inform the drug-associated risk. The background risk for major birth defects and miscarriage in patients with amyotrophic lateral sclerosis is unknown. In the U.S. general population, the background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

In studies in which riluzole was administered orally to pregnant animals, developmental toxicity (decreased embryofetal/offspring viability, growth, and functional development) was observed at clinically relevant doses *[see Data]*. Based on these results, women should be advised of a possible risk to the fetus associated with use of TIGLUTIK during pregnancy.

Data

Animal Data

Oral administration of riluzole (3, 9, or 27 mg/kg/day) to pregnant rats during the period of organogenesis resulted in decreases in fetal growth (body weight and length) at the high dose. The mid dose, a no-effect dose for embryofetal developmental toxicity, is approximately equal to the recommended human daily dose (RHDD, 100 mg) on a mg/m2 basis. When riluzole was administered orally (3, 10, or 60 mg/kg/day) to pregnant rabbits during the period of organogenesis, embryofetal mortality was increased at the high dose and fetal body weight was decreased and morphological variations increased at all but the lowest dose tested. The no-effect dose (3 mg/kg/day) for embryofetal developmental toxicity is less than the RHDD on a mg/m2 basis. Maternal toxicity was observed at the highest dose tested in rat and rabbit.

When riluzole was orally administered (3, 8, or 15 mg/kg/day) to male and female rats prior to and during mating and to female rats throughout gestation and lactation, increased embryofetal mortality and decreased postnatal offspring viability, growth, and functional development were observed at the high dose. The mid dose, a no-effect dose for pre- and postnatal developmental toxicity, is approximately equal to the RHDD on a mg/m2 basis.

8.2 Lactation

Risk Summary

It is not known if riluzole is excreted in human milk. Riluzole or its metabolites have been detected in milk of lactating rat. Women should be advised that many drugs are excreted in human milk and that the potential for serious adverse reactions in nursing infants from TIGLUTIK is unknown.

8.3 Females and Males of Reproductive Potential

In rats, oral administration of riluzole resulted in decreased fertility indices and increases in embryolethality *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

In clinical studies of riluzole, 30% of patients were 65 years and over. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Hepatic Impairment

Patients with mild [Child-Pugh's (CP) score A] or moderate (CP score B) hepatic impairment had increases in AUC compared to patients with normal hepatic function. Thus, patients with mild or moderate hepatic impairment may be at increased risk of adverse reactions. The impact of severe hepatic impairment on riluzole exposure is unknown.

Use of TIGLUTIK is not recommended in patients with baseline elevations of serum aminotransferases greater than 5 times upper limit of normal or evidence of liver dysfunction (e.g., elevated bilirubin) *[see Clinical Pharmacology (12.3)]*.

8.7 Japanese Patients

Japanese patients are more likely to have higher riluzole concentrations. Consequently, the risk of adverse reactions may be greater in Japanese patients *[see Clinical Pharmacology (12.3)]*.

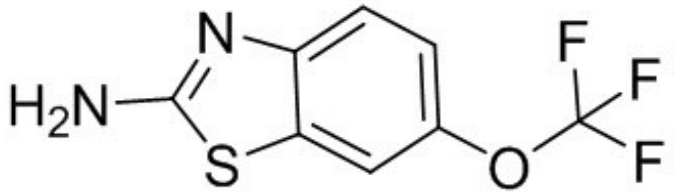
10 OVERDOSAGE

Reported symptoms of overdose following ingestion of riluzole ranging from 1.5 to 3 grams (30 to 60 times the recommended dose) included acute toxic encephalopathy, coma, drowsiness, memory loss, and methemoglobinemia.

No specific antidote for the treatment of TIGLUTIK overdose is available. For current information on the management of poisoning or overdosage, contact a certified poison control center.

11 DESCRIPTION

Riluzole is a member of the benzothiazole class. The chemical designation for riluzole is 2-amino-6-(trifluoromethoxy)benzothiazole. Its molecular formula is $C_8H_5F_3N_2OS$, and its molecular weight is 234.2. The chemical structure is:



Riluzole is a white to slightly yellow powder that is very soluble in dimethylformamide, dimethylsulfoxide, and methanol; freely soluble in dichloromethane; sparingly soluble in 0.1 N HCl; and very slightly soluble in water and in 0.1 N NaOH.

TIGLUTIK (50 mg/10mL) oral suspension is a slightly brown, opaque, homogeneous suspension containing 50 mg of riluzole per 10 mL of suspension.

TIGLUTIK also contains the following inactive ingredients: magnesium aluminum silicate, noncrystallizing sorbitol solution, polyoxyl 20 cetostearyl ether, purified water, saccharin sodium, simethicone emulsion, sodium lauryl sulfate, and xanthan gum.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism by which riluzole exerts its therapeutic effects in patients with ALS is unknown.

12.2 Pharmacodynamics

The clinical pharmacodynamics of riluzole has not been determined in humans.

12.3 Pharmacokinetics

Table 2 displays the pharmacokinetic parameters of riluzole.

Table 2. Pharmacokinetics of Riluzole[1]

Absorption	
Bioavailability (oral)	Approximately 60%
Dose Proportionality	Linear over a dose range of 25 mg to 100 mg every 12 hours (1/2 to 2 times the recommended dosage)
Food effect[2]	AUC ↓ 9% and Cmax ↓ 55% (high fat meal)
Time to peak plasma concentration (median)[2]	0.8 hours
Distribution	
Plasma Protein Binding	96% (Mainly to albumin and lipoproteins)
Elimination	
Elimination half-life	• 12 hours (CV=35%) • The high individual variability in the clearance of riluzole is potentially attributable to variability of CYP1A2. The clinical implications are not known.
Accumulation	Approximately 2-fold
Metabolism	
Fraction metabolized (% dose)	At least 88%
Primary metabolic pathway(s) [in vitro]	• Oxidation: CYP1A2 • Direct and sequential glucoronidation: UGT-HP4
Active Metabolites	Some metabolites appear pharmacologically active in vitro, but the clinical implications are not known.
Excretion	
Primary elimination pathways (% dose)	• Feces: 5% • Urine: 90% (2% unchanged riluzole)

[1] Unless otherwise stated, information in this table is based on pharmacokinetic studies of riluzole tablets.
[2] Information specific to TIGLUTIK

Specific Populations

Hepatic Impairment

Compared with healthy volunteers, the AUC of riluzole was approximately 1.7-fold greater in patients with mild chronic hepatic impairment (CP score A), and approximately 3-fold greater in patients with moderate chronic hepatic impairment (CP score B). The pharmacokinetics of riluzole have not been studied in patients with severe hepatic impairment (CP score C) *[see Use in Specific Populations (8.6)]*.

Race

The clearance of riluzole was 50% lower in male Japanese subjects than in Caucasian subjects, after normalizing for body weight *[see Use in Specific Populations (8.7)]*.

Gender

The mean AUC of riluzole was approximately 45% higher in female patients than male patients.

Smokers

The clearance of riluzole in tobacco smokers was 20% greater than in nonsmokers.

Geriatric Patients and Patients with Moderate to Severe Renal Impairment

Age 65 years or older and moderate to severe renal impairment do not have a meaningful effect on the pharmacokinetics of riluzole. The pharmacokinetics of riluzole in patients undergoing hemodialysis are unknown.

Drug Interaction Studies

Drugs Highly Bound To Plasma Proteins

Riluzole and warfarin are highly bound to plasma proteins. In vitro, riluzole did not show any displacement of warfarin from plasma proteins. Riluzole binding to plasma proteins was unaffected by warfarin, digoxin, imipramine and quinine at high therapeutic concentrations in vitro.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Riluzole was not carcinogenic in mice or rats when administered for 2 years at daily oral doses up to 20 and 10 mg/kg/day, respectively, which are approximately equal to the recommended human daily dose (RHDD, 100 mg) on a mg/m2 basis.

Mutagenesis

Riluzole was negative in *in vitro* (bacterial reverse mutation (Ames), mouse lymphoma tk, chromosomal aberration assay in human lymphocytes), and in *in vivo* (rat cytogenetic and mouse micronucleus) assays.

N-hydroxyriluzole, the major active metabolite of riluzole, was positive for clastogenicity in the in vitro mouse lymphoma tk assay and in the in vitro micronucleus assay using the same mouse lymphoma cell line. N-hydroxyriluzole was negative in the HPRT gene mutation assay, the Ames assay (with and without rat or hamster S9), the in vitro chromosomal aberration assay in human lymphocytes, and the in vivo mouse micronucleus assay.

Impairment of Fertility

When riluzole (3, 8, or 15 mg/kg) was administered orally to male and female rats prior to and during mating and continuing in females throughout gestation and lactation, fertility indices were decreased and embryolethality was increased at the high dose. This dose was also associated with maternal toxicity. The mid dose, a no-effect dose for effects on fertility and early embryonic development, is approximately equal to the RHDD on a mg/m2 basis.

14 CLINICAL STUDIES

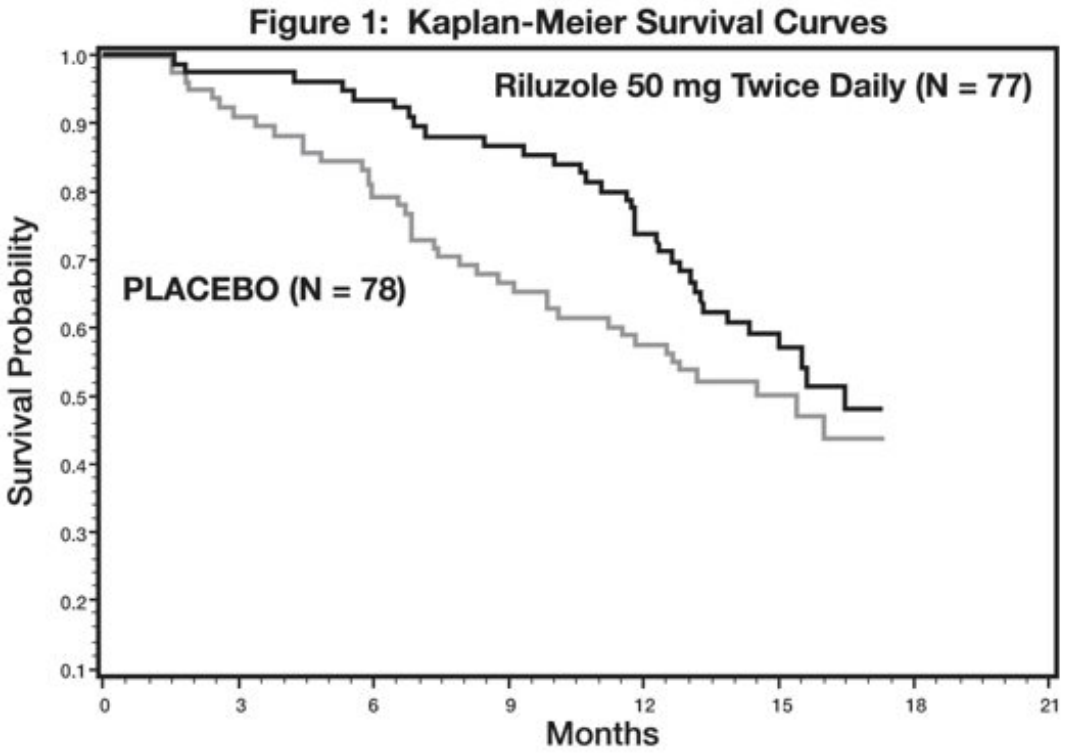
The efficacy of TIGLUTIK is based upon bioavailability studies comparing oral riluzole tablets to TIGLUTIK oral suspension *[see Clinical Pharmacology (12.3)]*.

The efficacy of riluzole was demonstrated in two studies (Study 1 and 2) that evaluated 50 mg riluzole oral tablets twice daily in patients with amyotrophic lateral sclerosis (ALS). Both studies included patients with either familial or sporadic ALS, disease duration of less than 5 years, and baseline forced vital capacity greater than or equal to 60% of normal.

Study 1 was a randomized, double-blind, placebo-controlled clinical study that enrolled 155 patients with ALS. Patients were randomized to receive riluzole 50 mg twice daily (n=77) or placebo (n=78) and were followed for at least 13 months (up to a maximum duration of 18 months). The clinical outcome measure was time to tracheostomy or death.

The time to tracheostomy or death was longer for patients receiving riluzole compared to placebo. There was an early increase in survival in patients receiving riluzole compared to placebo. Figure 1 displays the survival curves for time to death or tracheostomy. The vertical axis represents the proportion of individuals alive without tracheostomy at various times following treatment initiation (horizontal axis). Although these survival curves were not statistically significantly different when evaluated by the analysis specified in the study protocol (Logrank test p=0.12), the difference was found to be significant by another appropriate analysis (Wilcoxon test p=0.05). As seen in Figure 1, the study showed an early increase in survival in patients given riluzole. Among the patients in whom the endpoint of tracheostomy or death was reached during the study, the difference in median survival between the riluzole 50 mg twice daily and placebo groups was approximately 90 days.

Figure 1. Time to Tracheostomy or Death in ALS Patients in Study 1 (Kaplan-Meier Curves)

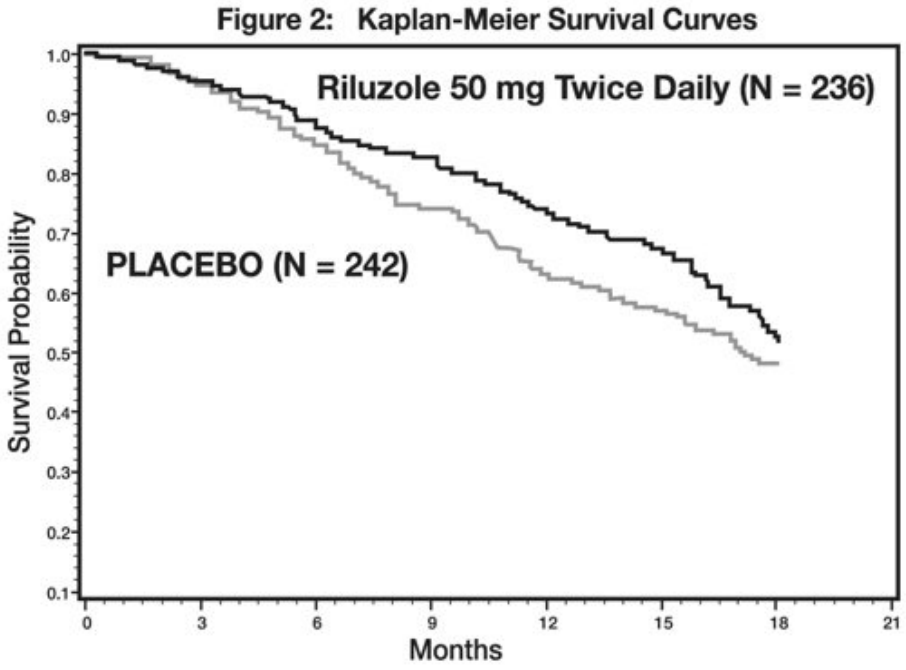


Study 2 was a randomized, double-blind, placebo-controlled clinical study that enrolled 959 patients with ALS. Patients were randomized to riluzole 50 mg twice daily (n=236) or placebo (n=242) and were followed for at least 12 months (up to a maximum duration of 18 months). The clinical outcome measure was time to tracheostomy or death.

The time to tracheostomy or death was longer for patients receiving riluzole compared to placebo. Figure 2 displays the survival curves for time to death or tracheostomy for patients randomized to either riluzole 100 mg per day or placebo. Although these survival curves were not statistically significantly different when evaluated by the analysis specified in the study protocol (Logrank test p=0.076), the difference was found to be significant by another appropriate analysis (Wilcoxon test p=0.05). Not displayed in Figure 2 are the results of riluzole 50 mg per day (one-half of the recommended daily dose), which could not be statistically distinguished from placebo, or the results of riluzole 200 mg per day (two times the recommended daily dose), which were not distinguishable from the 100 mg per day results. Among the patients in whom the endpoint of tracheostomy or death was reached during the study, the difference in median survival between riluzole and placebo was approximately 60 days.

Although riluzole improved survival in both studies, measures of muscle strength and neurological function did not show a benefit.

Figure 2. Time to Tracheostomy or Death in ALS Patients in Study 2 (Kaplan-Meier Curves)



16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

TIGLUTIK (50 mg/10 mL) oral suspension is supplied in amber glass bottles closed with child-resistant tamper evident screw caps. Each bottle contains 300 mL of oral suspension and is intended for multi-dose use, NDC 70726-0303-2.

TIGLUTIK is supplied in a carton, NDC 70726-0303-1, containing:

- Two bottles, each containing 300 mL oral suspension
- Two 10 mL oral syringes
- Two syringe bottle adapters
- Two syringe tip caps
- Prescribing Information, including Instructions for Use

16.2 Storage and Handling

Store at 20-25°C (68-77°F), excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature], and protect from bright light. Do not freeze. Store upright.

Use within 15 days after initially opening of each bottle. Discard any unused TIGLUTIK remaining after 15 days of first opening of the bottle.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Instructions for Use).

Administration Instructions

Instruct patients to discard any unused TIGLUTIK after 15 days of opening the bottle.

Hepatic Injury

Advise patients that TIGLUTIK can cause liver injury, which can be fatal.

Inform patients of the clinical signs or symptoms suggestive of hepatic dysfunction (e.g., unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine) and to contact a healthcare provider promptly if these signs or symptoms occur *[see Warnings and Precautions (5.1)]*.

Neutropenia

Advise patients that TIGLUTIK can cause neutropenia, and to report to their healthcare provider if they have a fever *[see Warnings and Precautions (5.2)]*.

Interstitial Lung Disease

Advise patients that TIGLUTIK can cause interstitial lung disease, and to report to their healthcare provider if they have respiratory symptoms (e.g., dry cough and difficult or labored breathing) *[see Warnings and Precautions (5.3)]*.

Manufactured for:
ITF Pharma, Inc.
850 Cassatt Road, Suite 350
Berwyn, PA 19312 USA

Instructions for Use

TIGLUTIK™ (TIG loo tick)

(riluzole)

50 mg/10 mL oral suspension

Read this Instructions for Use before you start taking TIGLUTIK and each time you get a refill. There may be new information. This leaflet does not take the place of talking to your healthcare provider about your medical condition or treatment.

Important information about measuring TIGLUTIK:

Always use the oral syringe that comes with TIGLUTIK to measure your prescribed dose. Ask your healthcare provider or pharmacist to show you how to measure your prescribed dose.

Each TIGLUTIK carton contains:

- 2 TIGLUTIK bottles
- 2 bottle adapters
- 2 10 mL oral syringes
- 2 syringe tip caps

Use a new 10 mL oral syringe, bottle adapter, and syringe tip cap when using a new bottle of TIGLUTIK (see Figure A).

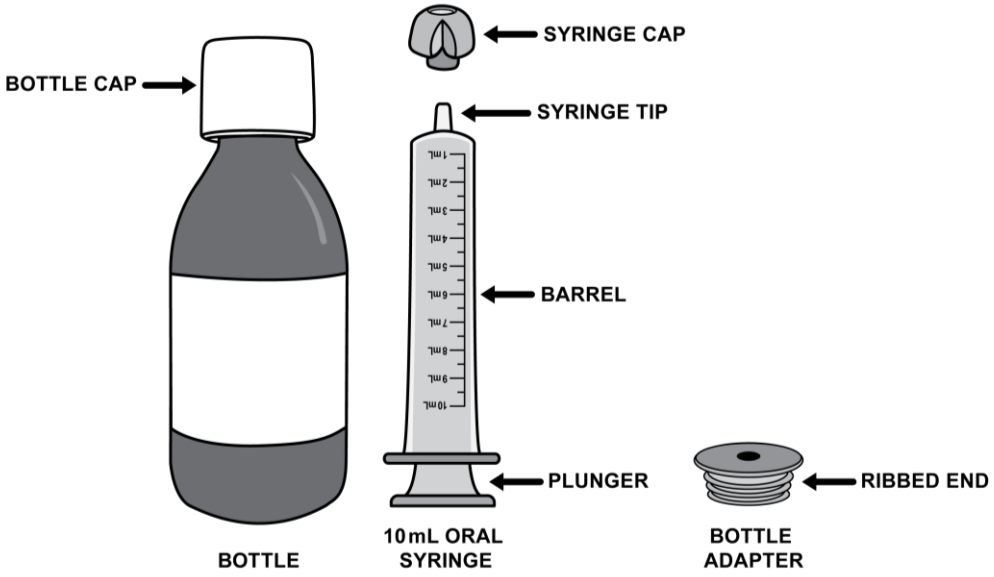


Figure A

Important information:

- Keep these instructions for future use.
- Do not share TIGLUTIK with anyone else.
- Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.
- People who have problems using their hands may need assistance to draw up and give the correct dose of TIGLUTIK.

How to take TIGLUTIK:

- Take TIGLUTIK as prescribed by your healthcare provider. The recommended dose of TIGLUTIK is 50 mg (10 mL) taken by mouth 2 times each day, every 12 hours.
- Take TIGLUTIK at least 1 hour before or 2 hours after a meal.
- Take TIGLUTIK using a 10 mL oral syringe that comes with TIGLUTIK.

Step 1. First time use of bottle only: Remove one TIGLUTIK bottle, one bottle adapter, one 10 mL oral syringe and one syringe tip cap from the carton (see Figure A above).

Step 2. Gently shake the bottle **for at least 30 seconds** by continuously turning the bottle up and down until the TIGLUTIK suspension is mixed well and you do not see any clear liquid at the top of the suspension or any particles at the bottom of the bottle (see Figure B).

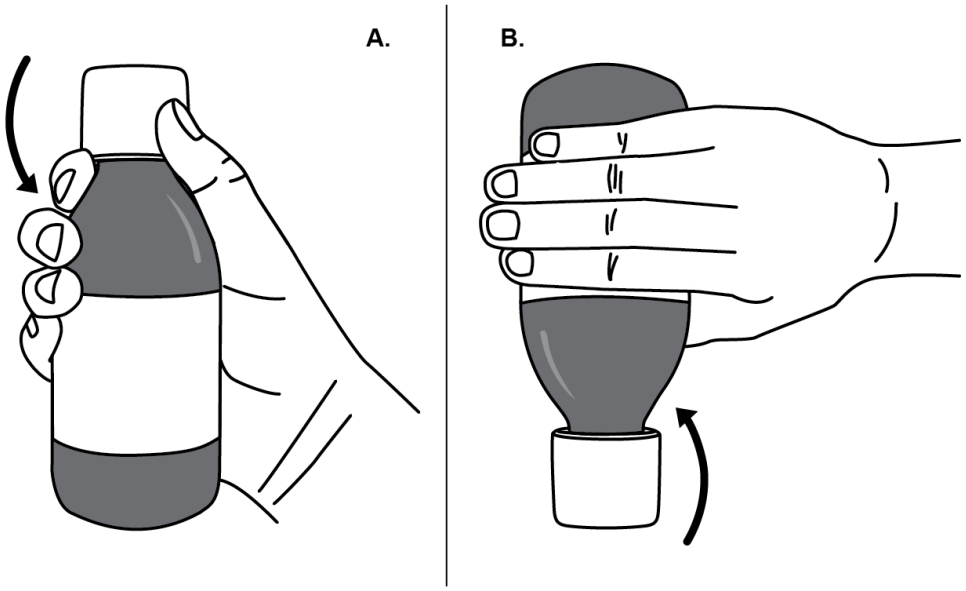


Figure B

Step 3. Open the bottle by pressing down on the bottle cap and turning it counterclockwise (to the left) (see Figure C).

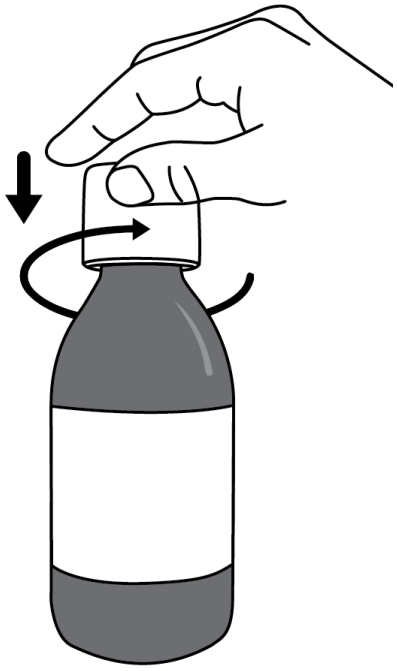


Figure C

Step 4. First time use of bottle only: Place the open bottle upright on a flat surface. Insert the ribbed end of the bottle adapter into the bottle by firmly pressing it in as far as it will go (see Figure D). **Do not** remove the bottle adapter from the bottle after it is inserted.

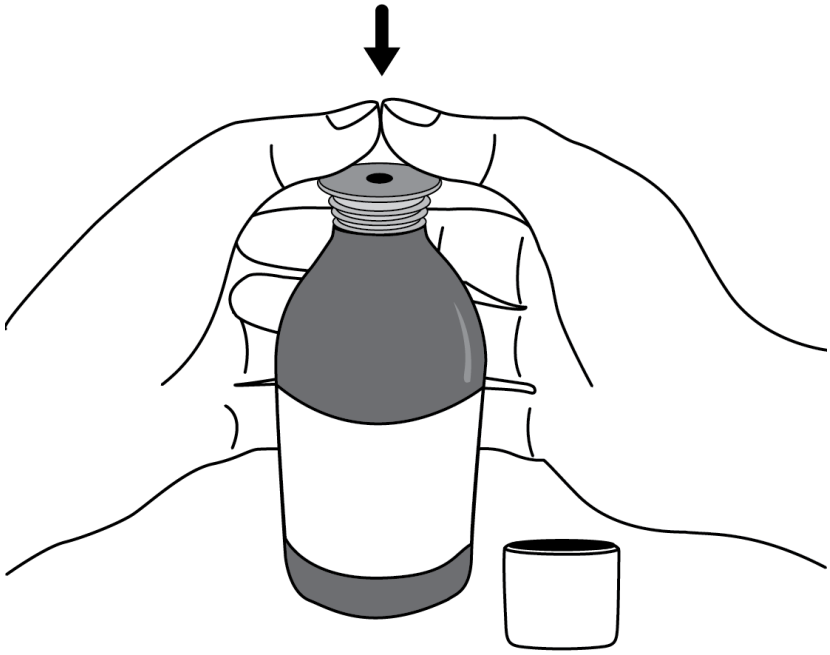


Figure D

Step 5. Push the plunger of the 10 mL oral syringe all the way in to remove air from the oral syringe (see Figure E).

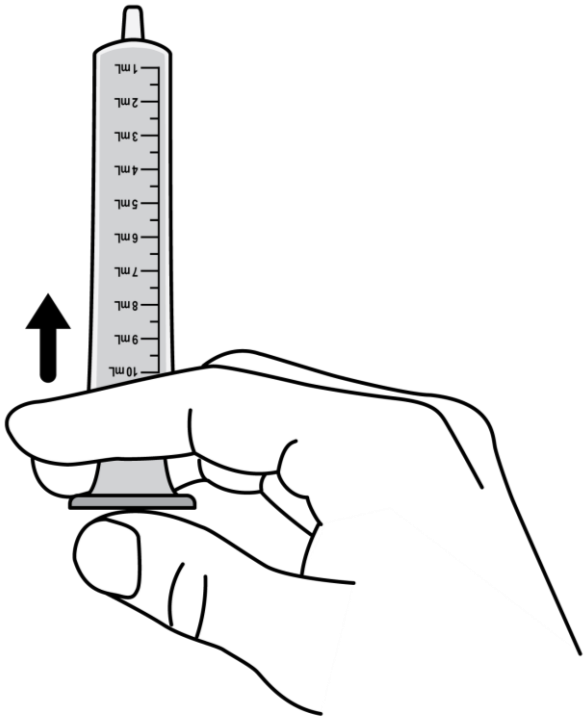


Figure E

Step 6. Insert the 10 mL oral syringe into the opening of the bottle adapter until the oral syringe is firmly in place (see Figure F).

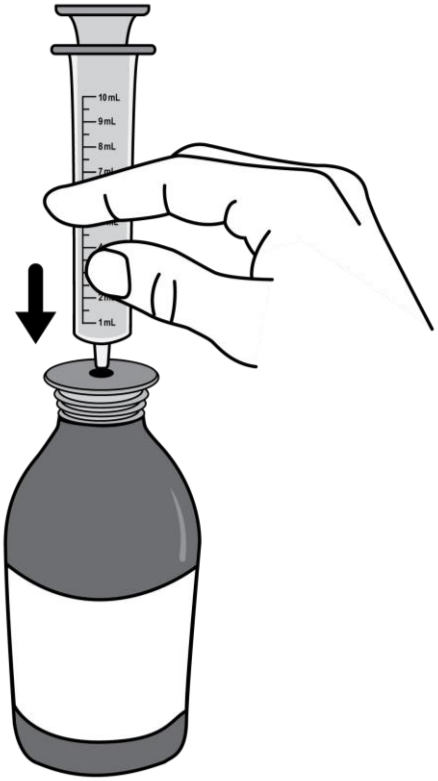


Figure F

Step 7. Turn the bottle upside down. Slowly pull the plunger down to withdraw a small amount of the suspension. Then push the plunger all the way in to remove any air bubbles (see Figure G).

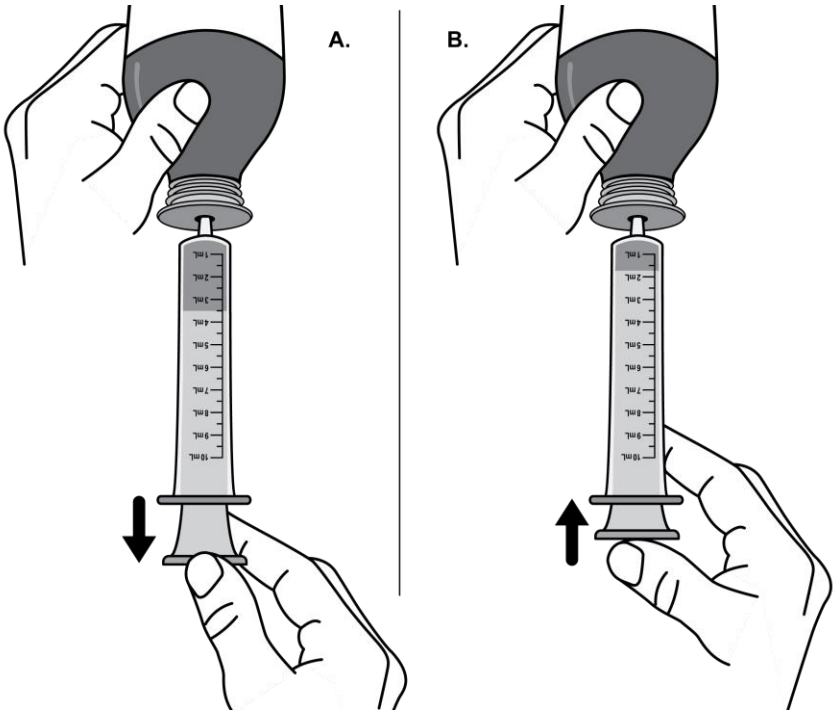


Figure G

Step 8. Slowly pull the plunger down to the 10 mL marking on the oral syringe (see Figure H).

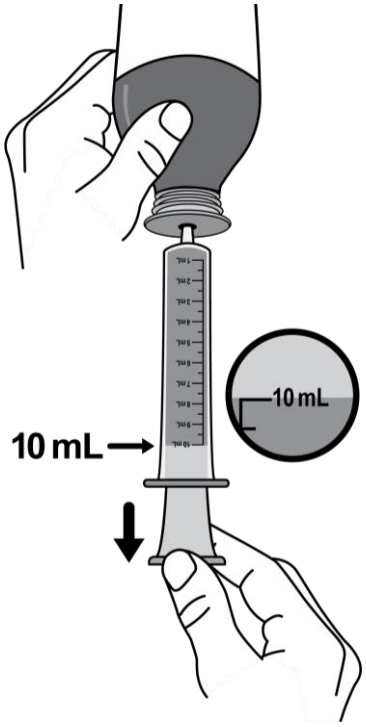


Figure H

Step 9. While keeping the plunger in the same position, turn the bottle upright, and place it carefully on a flat surface. Remove the oral syringe by **gently** twisting or pulling it out from the bottle adapter (see Figure I).

Figure I

Step 10. Check that 10 mL of TIGLUTIK has been drawn up into the oral syringe (see Figure J).

If the dose is not correct, insert the oral syringe tip firmly into the bottle adapter. Push the plunger all the way in so that the TIGLUTIK solution flows back into the bottle. Turn the bottle upside down. Repeat Steps 8 and 9.

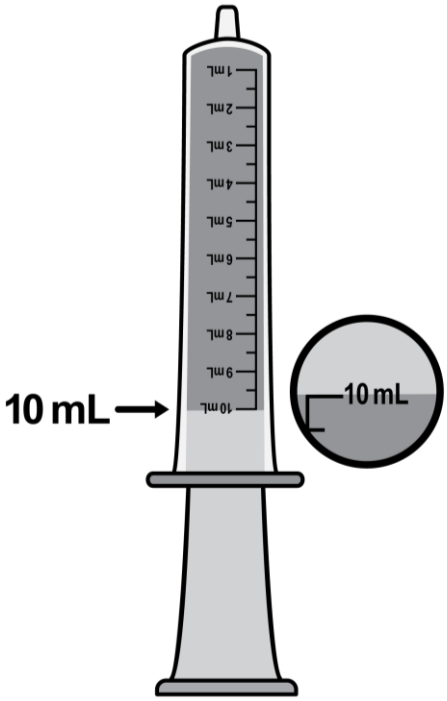


Figure J

Step 11. Place the tip of the oral syringe in your mouth and aim the tip toward the inside of your cheek. Slowly push the plunger all the way in until the oral syringe is empty (see Figure K).

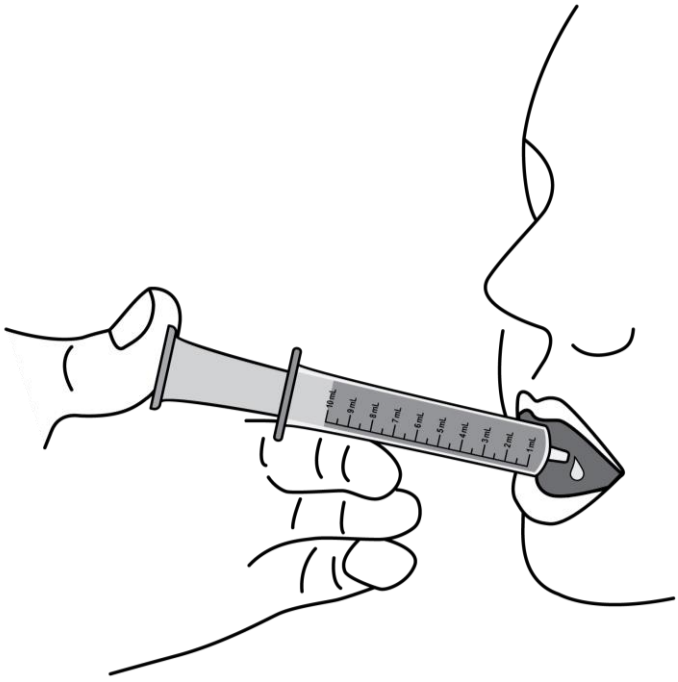


Figure K

Step 12. Leave the adapter in the bottle. Place the bottle cap on the bottle and turn the bottle cap clockwise (to the right) to close the bottle (see Figure L).

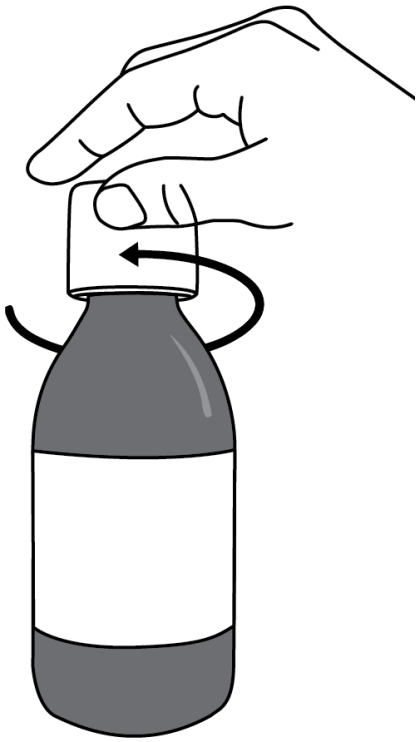


Figure L

Step 13. Remove the plunger from the oral syringe barrel. Rinse the oral syringe barrel, plunger, and syringe tip cap with water.

When the oral syringe barrel, plunger, and syringe tip cap are dry, put the plunger back into the oral syringe barrel and put the syringe tip cap on the syringe tip. **Do not throw away the oral syringe.** Keep this oral syringe for use with this bottle of TIGLUTIK (see Figure M).

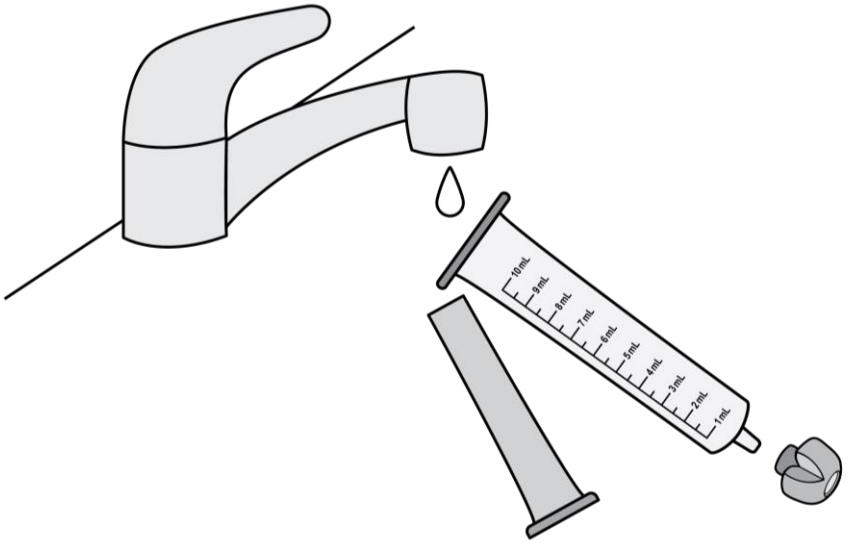


Figure M

Step 14. Store the oral syringe in a clean, dry place.

How to store TIGLUTIK:

- Store TIGLUTIK at room temperature between 68°F to 77°F (20°C to 25°C).
- Do not freeze TIGLUTIK.
- Store TIGLUTIK upright and protect from bright light.
- After opening the bottle of TIGLUTIK, use within 15 days. **Throw away (dispose of) any TIGLUTIK that is not used within 15 days after opening the bottle.** Write the date you open the bottle on the bottle label. Ask your pharmacist how to properly throw away (dispose of) medicines you no longer use.
- Do not use TIGLUTIK after the expiration date (EXP) on the carton and the bottle. The expiration date is the last day of the expiration month.
- Open a new bottle of TIGLUTIK when you are ready to give the first dose.
- Keep bottle tightly closed between each use.
- **Keep TIGLUTIK and all medicines out of the sight and reach of children.**

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured for:
ITF Pharma, Inc.
850 Cassatt Road, Suite 350
Berwyn, PA 19312 USA

Issued: 9/2018

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ERIC P BASTINGS
09/05/2018