February 2024

IMPORTANT PRESCRIBING INFORMATION

Subject: Temporary importation of TEGLUTIK (riluzole oral suspension, 5 mg/mL) with non-English labeling to address drug shortage in the United States

Dear Health Care Provider,

The purpose of this letter is to inform you about a temporary importation in the United States (U.S.) of TEGLUTIK (riluzole 5 mg/mL oral suspension) with bottle and carton labels in Spanish, in coordination with the U.S. Food and Drug Administration (FDA) to mitigate the current shortage of FDA-approved Tiglutik (riluzole oral suspension, 50 mg/10 mL) in the U.S. This temporary supply of TEGLUTIK is marketed and manufactured by Italfarmaco in Spain and is not FDA-approved.

Riluzole is indicated for the treatment of amyotrophic lateral sclerosis (ALS). Recently, Tiglutik was recalled in the U.S. market due to an out-of-specification test result for viscosity.

At this time, no other entity except EDW Pharma, Inc. (formerly Italfarmaco (ITF) Pharma, Inc.) is authorized by the FDA to import or distribute Italfarmaco's TEGLUTIK riluzole oral suspension in the U.S.

Effective immediately, and during this temporary period, EDW Pharma, Inc. will distribute the following presentation of riluzole oral suspension to address the critical shortage:

Product Name	Quantity	Description	U.S. NDC Number	Lot Number	Expiration Date
TEGLUTIK riluzole oral suspension (5 mg/mL)	1 bottle per carton	Teglutik is presented as a slightly brown, opaque homogeneous oral suspension after being manually gently shaken. TEGLUTIK is available in a bottle of 300 ml with a plastic graduated oral dosing syringe. The syringe barrel is graduated in milliliters up to 10 ml.	70726-0305-1	23026	12-2026

The safety profiles of the FDA-approved Tiglutik and imported TEGLUTIK products are comparable and no specific safety concerns emerged from the comparison of the two products.

Please refer to the side-by-side comparison of the labels (enclosed) for additional information.

It is important to note that the enclosed side-by-side comparisons, in English, between the U.S. product information and the European product information including the labels, patient leaflet, and SmPC (Summary of Product Characteristics, equivalent to the U.S. Prescribing Information (USPI)) have been included to also provide all applicable information since the labels and leaflet with the imported product are in Spanish.

Tiglutik is available only by prescription in the U.S. The imported lot does not have the statement "Rx only" on its labeling.

The barcode on the imported product label may not register accurately on the U.S. scanning systems. Institutions should manually input the imported product information into their systems and confirm that the barcode, if scanned, provides correct information. Alternative procedures should be followed to assure that the correct drug product is being used and administered to individual patients.

In addition, the package of the imported product does not include a product identifier as required under the Drug Supply Chain Security Act (DSCSA). Specifically, each package does not include the NDC, unique serial number, lot number, and expiration date in both human-readable and a two-dimensional data matrix barcode. Additionally, the imported product may not be accompanied with DSCSA-required product tracing documentation (transaction information, transaction history, and transaction statement).

Reporting Adverse Events

Health care providers and patients are encouraged to report adverse events and medication errors in patients taking TEGLUTIK to AnovoRx at 1-844-763-1198. You are encouraged to report negative side effects of prescription drugs to the FDA.

Adverse events or quality problems experienced with the use of this product may also be reported to the FDA's MedWatch Adverse Event Reporting Program either online, by regular mail, or by fax:

- Complete and submit the report Online: www.fda.gov/medwatch/report.htm
- Regular mail or Fax: Download form www.fda.gov/MedWatch/getforms.htm or call 1-800-332-1088 to request a reporting form, then complete and return to the address on the pre-addressed form or submit by fax to 1-800-FDA-0178 (1-800-332-0178).

You may also contact AnovoRx at 1-844-763-1198 if you have any questions about the information contained in this letter or the safe and effective use of TEGLUTIK.

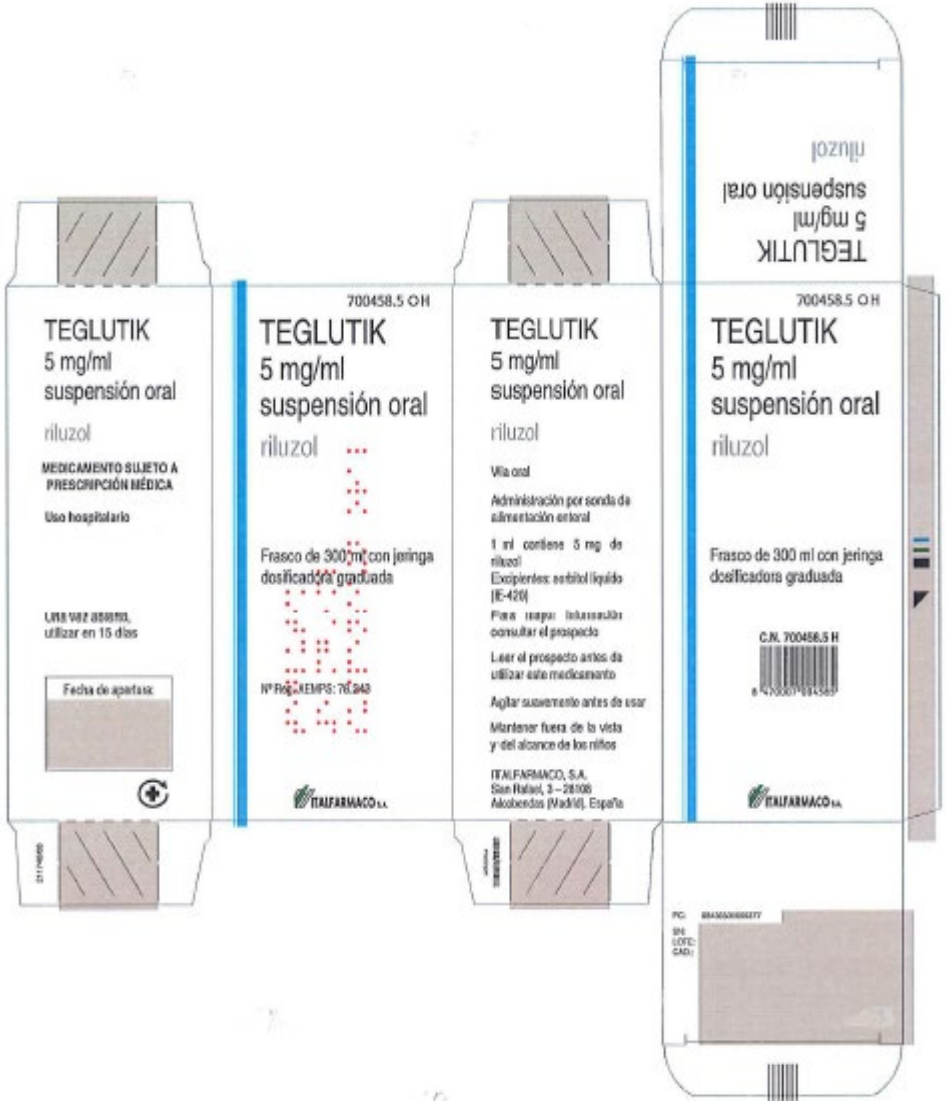
This letter is not intended as a complete description of the benefits and risks related to the use of TEGLUTIK. Please refer to the enclosed TEGLUTIK SmPC and Tiglutik USPI side-by-side comparison.

For additional information, please visit www.tiglutik.com and www.edwpharma.com.

Sincerely,

Peter Cook
CEO and President
EDW Pharma, Inc. *(Formerly ITF Pharma, Inc.)*

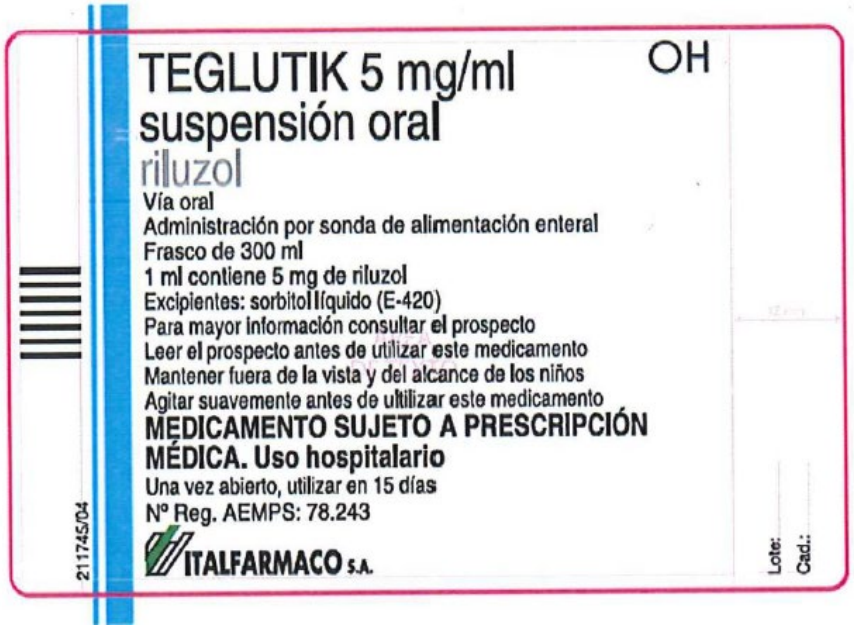
Enclosures:
1 – TEGLUTIK and Tiglutik side-by-side comparison of the bottle and carton labels
2 – TEGLUTIK SmPC and Tiglutik USPI side-by-side comparison
3 – TEGLUTIK and Tiglutik side-by-side comparison of the patient leaflet

IMPORTED PRODUCT (SPANISH CARTON - IMAGE)	FDA-APPROVED PRODUCT (U.S. CARTON - IMAGE)
	

(ENGLISH TRANSLATION OF SPANISH CARTON - TEXT)	(U.S. CARTON - TEXT)
NAME OF THE MEDICINAL PRODUCT TEGLUTIK 5 mg/ml oral suspension riluzole	**NAME OF THE MEDICINAL PRODUCT** TIGLUTIK® riluzole oral suspension 50mg/10ml(5mg/ml)
STATEMENT OF ACTIVE SUBSTANCE(S) 1 ml contains: 5 mg of riluzole	**STATEMENT OF ACTIVE SUBSTANCE(S)** Contains: TIGLUTIK® 50 mg/10 mL (5 mg/mL)
LIST OF EXCIPIENTS Also contains: liquid sorbitol (E420) For more information read the package leaflet.	-------
PHARMACEUTICAL FORM AND CONTENTS Oral suspension Bottle of 300 ml with a graduated dosing syringe	**PHARMACEUTICAL FORM AND CONTENTS** 600 mL (two bottles/300 mL each) Not To Be Dispensed Separately This product is a liquid suspension and is supplied with syringes for oral administration. Before use, please read the enclosed Prescribing Information. TIGLUTIK® 50 mg/10 mL (5 mg/mL) oral suspension is a slightly brown, opaque, homogeneous suspension when mixed, containing 50 mg of riluzole per 10 mL of suspension
METHOD AND ROUTE(S) OF ADMINISTRATION Read the package leaflet before use Oral use Administration via enteral feeding tube Shake gently before use	**METHOD AND ROUTE(S) OF ADMINISTRATION** For oral administration Shake gently before use The bottle must be gently shaken for at least 30 seconds by continuously rotating the bottle 180° until the visual appearance of the suspension is homogeneous.
DOSAGE	**DOSAGE**

----------	The recommended dose is 10 mL of TIGLUTIK® oral suspension, containing 50 mg of riluzole, taken orally twice daily, every 12 hours.
SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN Keep out of the sight and reach of children	**SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN** Keep out of reach of children.
OTHER SPECIAL WARNING ------	**OTHER SPECIAL WARNING** **Pharmacist:** Please dispense TIGLUTIK® using the two 300 mL bottles enclosed, without breaking open bottle seals.
SPECIAL STORAGE CONDITIONS Expiry: Once opened, use within 15 days	**SPECIAL STORAGE CONDITIONS** Store TIGLUTIK® at controlled room temperature between 20°-25°C (68°-77°F), excursions permitted to 15°-30°C (59°-86°F) and protect from bright light. Do not freeze. Store upright. Once opened, the bottle of TIGLUTIK® should be used within 15 days. Keep bottle tightly closed between each use.
----------	**CONTENT OF THIS PACKAGE** Two bottles, each containing 300 mL Two 10 mL oral syringes Two syringe bottle adapters Two siringe tip caps One Prescribing Information, including Instruction for Use

GENERAL CLASSIFICATION FOR SUPPLY Medicinal product subject to medical prescription Hospital use	**GENERAL CLASSIFICATION FOR SUPPLY** Rx only
NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER ITALFARMACO, S.A. C/ San Rafael, 3 – 28108 Alcobendas (Madrid). España	**ITF Pharma** Manufactured for: ITF Pharma, Inc. Berwyn, PA 19312 USA TIGLUTIK is a registered trademark of Italfarmaco S.A. TOCXXXXXX

IMPORTED PRODUCT (SPANISH BOTTLE LABEL - IMAGE)	FDA-APPROVED PRODUCT (U.S. BOTTLE LABEL - IMAGE)
	
(ENGLISH TRANSLATION OF SPANISH BOTTLE LABEL - TEXT)	**(U.S. BOTTLE LABEL - TEXT)**
NAME OF THE MEDICINAL PRODUCT TEGLUTIK 5 mg/ml oral suspension riluzole	**NAME OF THE MEDICINAL PRODUCT** TIGLUTIK® riluzole oral suspension 50mg/10ml(5mg/ml)
STATEMENT OF ACTIVE SUBSTANCE(S) 1 ml contains: 5 mg of riluzole	**STATEMENT OF ACTIVE SUBSTANCE(S)** Contains: TIGLUTIK® 50 mg/10 mL (5 mg/mL)

LIST OF EXCIPIENTS Also contains: liquid sorbitol (E420) For more information read the package leaflet.	-------
PHARMACEUTICAL FORM AND CONTENTS Oral suspension Bottle of 300 ml	**PHARMACEUTICAL FORM AND CONTENTS** TIGLUTIK® 50 mg/10 mL (5 mg/mL) oral suspension is a slightly brown, opaque, homogeneous suspension when mixed, containing 50 mg of riluzole per 10 mL of suspension
METHOD AND ROUTE(S) OF ADMINISTRATION Read the package leaflet before use Oral use Administration via enteral feeding tubes Shake gently before use	**METHOD AND ROUTE(S) OF ADMINISTRATION** Before use, please read the enclosed Prescribing Information. For oral administration Shake gently before use The bottle must be gently shaken for at least 30 seconds by continuously rotating the bottle 180° until the visual appearance of the suspension is homogeneous.
DOSAGE **-----**	**DOSAGE** The recommended dose is 10 mL of TIGLUTIK® oral suspension, containing 50 mg of riluzole, taken orally twice daily, every 12 hours.
SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN Keep out of the sight and reach of children	**SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN** Keep out of reach of children.
SPECIAL STORAGE CONDITIONS Expiry: Once opened, use within 15 days	**SPECIAL STORAGE CONDITIONS** Store TIGLUTIK® at controlled room temperature between 20°-25°C (68°-77°F), excursions permitted to 15°-30°C (59°-86°F) and protect from bright light. Do not freeze. Store upright. Once opened, the bottle of TIGLUTIK® should be used within 15 days. Keep bottle tightly closed between each use.

GENERAL CLASSIFICATION FOR SUPPLY Medicinal product subject to medical prescription Hospital use	**GENERAL CLASSIFICATION FOR SUPPLY** Rx only
NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER ITALFARMACO S.A	**ITF Pharma** Manufactured for: ITF Pharma, Inc. Berwyn, PA 19312 USA TIGLUTIK is a registered trademark of Italfarmaco S.A. TOCXXXXXX

IMPORTED PRODUCT **PACKAGE LEAFLET: INFORMATION FOR THE USER (SPAIN)** **(ENGLISH TRANSLATION)**	**FDA-APPROVED PRODUCT** **INSTRUCTIONS FOR USE (U.S.)**
TEGLUTIK 5 MG/ML ORAL SUSPENSION riluzole	TIGLUTIK® (TIG loo tick) (riluzole) 50 mg/10 mL oral suspension
Read all of this leaflet carefully before you start taking this medicine because it contains important information for you. • Keep this leaflet. You may need to read it again. • If you have any further questions, ask your doctor or pharmacist. • This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours. • If you get any side effects, talk to your doctor pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.	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:** • 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.
WHAT IS IN THIS LEAFLET: **1.** What TEGLUTIK is and what it is used for 2. What you need to know before you take TEGLUTIK 3. How to take TEGLUTIK 4. Possible side effects 5. How to store TEGLUTIK 6. Contents of the pack and other information	

1. What TEGLUTIK is and what it is used for

What TEGLUTIK is

The active substance in TEGLUTIK is riluzole which acts on the nervous system.

What TEGLUTIK is used for

TEGLUTIK is used in patients with amyotrophic lateral sclerosis (ALS). ALS is a form of motor neurone disease where attacks of the nerve cells responsible for sending instructions to the muscles lead to weakness, muscle waste and paralysis.

The destruction of nerve cells in motor neurone disease may be caused by too much glutamate (a chemical messenger) in the brain and spinal cord. TEGLUTIK stops the release of glutamate and this may help in preventing the nerve cells being damaged.

Please consult your doctor for more information about ALS and the reason why this medicine has been prescribed for you.

2. What you need to know before you take TEGLUTIK

Do not take TEGLUTIK

- if you are **allergic** to riluzole or any of the other ingredients of this medicine (listed in section 6),
- if you have any **liver disease** or increased blood levels of some enzymes of the liver (**transaminases**),
- if you are **pregnant or breast-feeding.**

Warnings and precautions

Talk to your doctor or pharmacist before taking TEGLUTIK:

- if you have any **liver problems:** yellowing of your skin or the white of your eyes (jaundice), itching all over, feeling sick, being sick;
- if your **kidneys** are not working very well;
- if you have any **fever:** it may be due to a low number of white blood cells which can cause an increased risk of infection;

If any of the above applies to you, or if you are not sure, tell your doctor who will decide what to do. **Children and Adolescents** If you are less than 18 years of age, the use of TEGLUTIK is not recommended because there is no information available in this population. **Other medicines and TEGLUTIK** Tell your doctor if you are taking, have recently taken or might take any other medicines. **Pregnancy, breast-feeding and fertility** You **must not** take TEGLUTIK if you are pregnant, think you may be pregnant, or if you are breast feeding. If you think you may be pregnant or if you intend to breast-feed, ask your doctor for advice before taking this medicine. **Driving and using machines** You can drive or use any tools or machines, unless you feel dizzy or light headed after taking this medicine. **TEGLUTIK contains liquid sorbitol (E420) and sodium.** This medicine contains 4000 mg sorbitol (E420) in 10 ml of oral suspension. Sorbitol is a source of fructose. If your doctor has told you that you have an intolerance to some sugars or if you have been diagnosed with hereditary fructose intolerance (HFI), a rare genetic disorder in which a person cannot break down fructose, talk to your doctor before you take this medicine. This medicine contains less than 1 mmol sodium (23 mg) per 10 ml of oral suspension, that is to say essentially 'sodium-free' see section 4.3, section 4.4, and section 5.2.	
3. How to take TEGLUTIK The suspension can be given per oral administration and alternatively it is also suitable for administration via enteral feeding tubes.	**How to take TIGLUTIK:** • Take TIGLUTIK as prescribed by your healthcare provider. The recommended dose of TIGLUTIK is 50 mg (10 mL) 2 times each day, every

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.
The recommended dose is 100 mg a day (50 mg every 12 hours).10 ml of the oral suspension, containing 50 mg of riluzole, should be taken by mouth every 12 hours, at the same time of the day each day (for example, in the morning and evening).The suspension is administered by means of graduated dosing syringe.

The oral suspension must be manually gently shaken for at least 30 seconds by continuously turning the bottle up and down until the TEGLUTIK 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.

Method of administration:

Instructions for oral use:
Open the bottle: press the cap and turn it anticlockwise (figure 1)

Take the syringe, remove the tip and insert the syringe in the adaptor opening (figure 2). Turn the bottle upside down (figure 3).

12 hours.

- TIGLUTIK can be taken by mouth or it can be given through a percutaneous endoscopic gastrostomy (PEG) tube. Both silicone and polyurethane PEG tubes can be used.
- 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.

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).

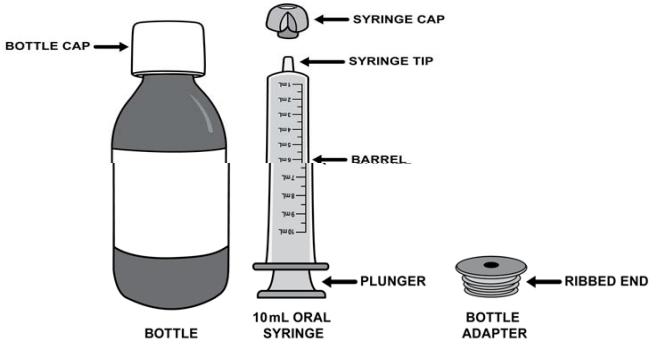
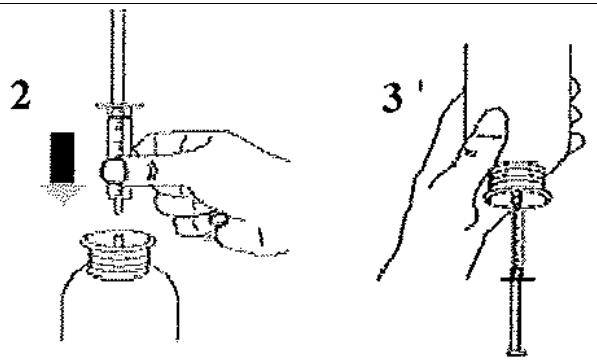
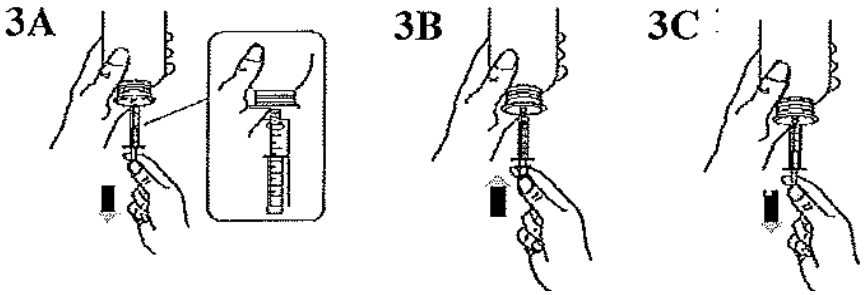


Figure A



Fill the syringe with a small amount of suspension by pulling the plunger down (figure 3A), then push the piston upward in order to remove any possible bubble (figure 3B). Pull the piston down to the graduation mark corresponding to the quantity in milliliters (ml) prescribed by your doctor (figure 3C).



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).

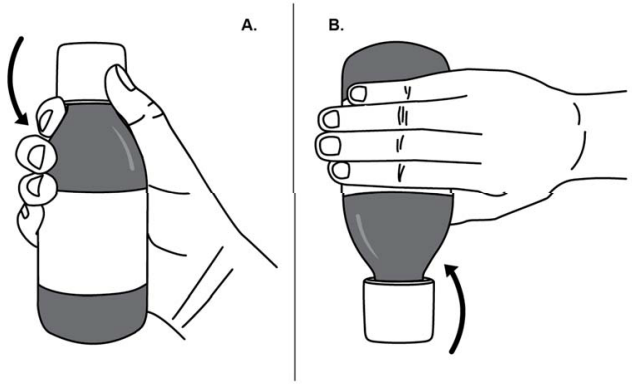


Figure B

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

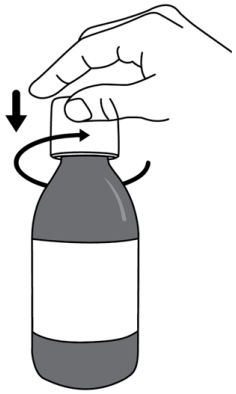
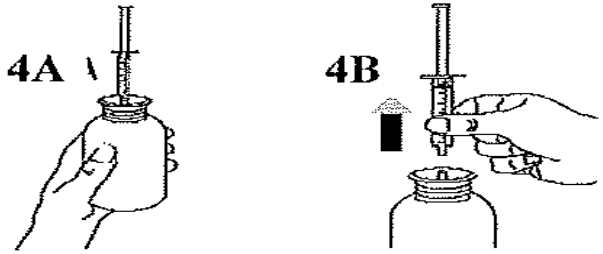
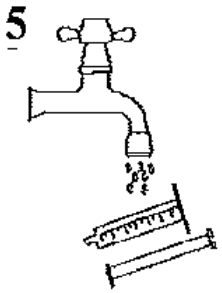


Figure C

Turn the bottle the right way up (figure 4A). Remove the syringe from the adaptor (figure 4B).



- Administer orally the whole content of the syringe.
- Close the bottle with the plastic screw cap.
- Wash the syringe with water only and re-assemble it with its tip cap once dried (figure 5).



<u>Instructions for use via enteral feeding tubes:</u>

<u>Ensure that the enteral feeding tube is free from obstruction before</u>

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.

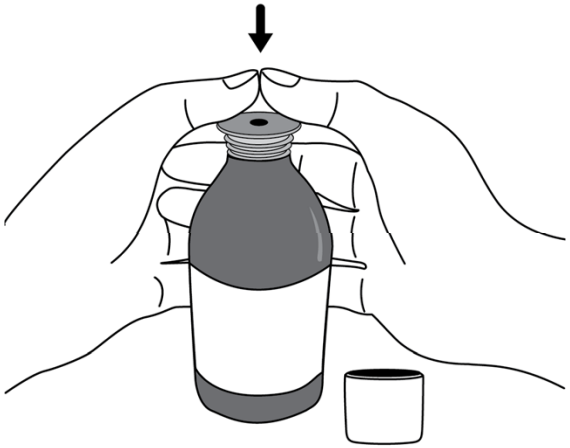


Figure D

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).

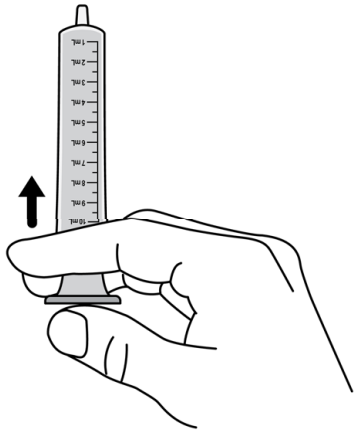


Figure E

administration.

1. Flush the enteral tube with 30 ml of water

2. Administer the required dose of Teglutik oral suspension with a graduated dosing syringe

3. Flush the enteral tube with 30 ml of water

If you take more TEGLUTIK than you should

If you take too much suspension, contact your doctor or the nearest hospital emergency department immediately.

If you forget to take TEGLUTIK

If you forget to take your dose, leave out that dose completely and take the next dose at the usual time.
Do not take a double dose to make up for a forgotten dose.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

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).

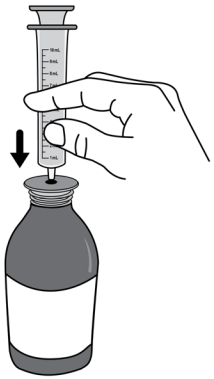


Figure F

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).

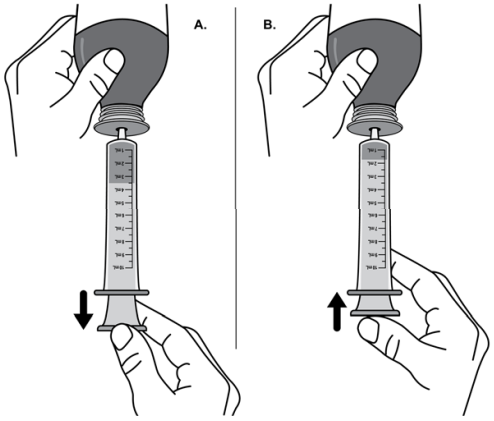


Figure G

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

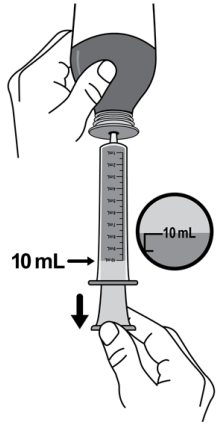


Figure H

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).

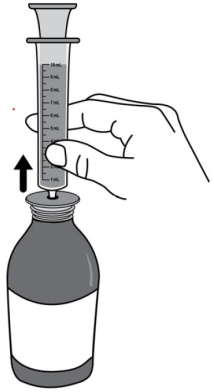


Figure I

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.

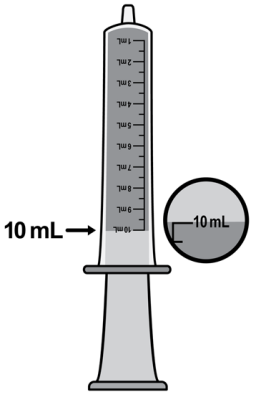


Figure J

If you are taking your dose of TIGLUTIK by mouth, follow the instructions in **"How to take a dose of TIGLUTIK oral suspension by mouth".**

If you are taking your dose of TIGLUTIK through a Percutaneous Endoscopic Gastrostomy (PEG) tube, follow the instructions in "How to take a dose of TIGLUTIK oral suspension through a Percutaneous Endoscopic Gastrostomy (PEG) tube".

How to take a dose of Tiglutik oral suspension by mouth:
Step 1. Place the tip of the oral syringe (containing the 10mL of Tiglutik) 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).

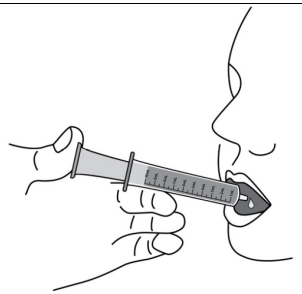


Figure K

Step 2. 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).

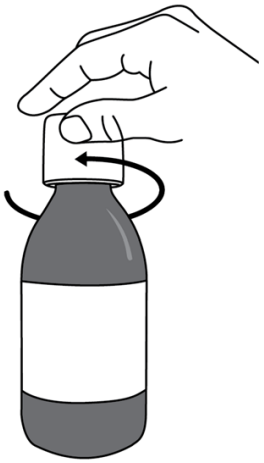


Figure L

Step 3. 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)**.**

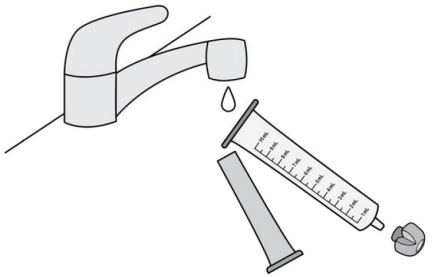


Figure M

Step 4. Store the oral syringe in a clean, dry place.

Y**ou must complete Steps 1 through 10 under "How to take TIGLUTIK" before starting Step 1 under "How to take a dose of TIGLUTIK oral suspension through a Percutaneous Endoscopic Gastrostomy (PEG) tube." How to take a dose of TIGLUTIK oral suspension through a Percutaneous Endoscopic Gastrostomy (PEG) tube:**

Step 1. Using a catheter-tip syringe, flush the PEG-tube with 1 ounce (30 mL) of water (see Figure N).

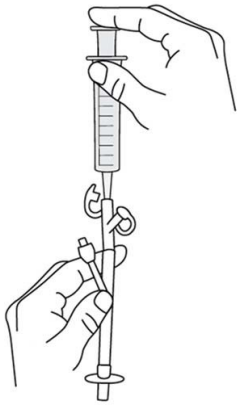


Figure N

Step 2. Place the oral syringe provided (containing the 10 mL of TIGLUTIK) into the PEG tube right away. Slowly push down the plunger until the oral syringe is empty (see Figure O).

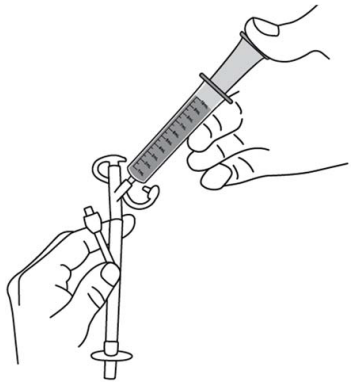


Figure O

Step 3. Using a catheter-tip syringe, flush the PEG tube a second time with 1 ounce (30 mL) of water (see Figure P).

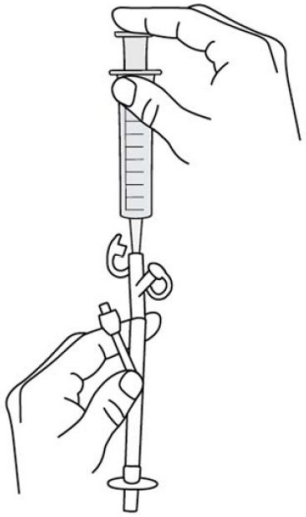


Figure P

Step 4. 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 Q).

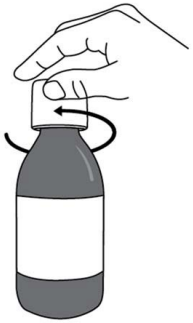


Figure Q

Step 5. 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 R).

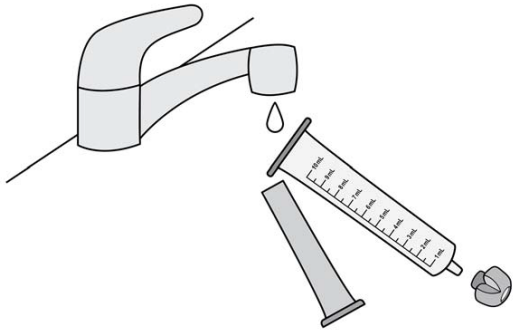


Figure R

Step 6. Store the oral syringe in a clean, dry place.

4. Possible side effects

Like all medicines, TEGLUTIK can cause side effects, although not everybody gets them.

Important
Tell your doctor immediately

- if you experience any **fever** (increase in temperature) because TEGLUTIK may cause a decrease in the number of white blood cells. Your doctor may want to take a blood sample to check the number of white blood cells, which are important in fighting infections.

- if you experience any of the following symptoms: yellowing of your skin or the white of your eyes (jaundice), itching all over, feeling sick, being sick, as these may be signs of **liver disease** (hepatitis).Your doctor may do regular blood tests while you are taking TEGLUTIK to make sure that this does not occur.

- if you experience cough or difficulties in breathing, as this may be a sign of **lung disease** (called interstitial lung disease).

Other side effects

Very common side effects (may affect more than 1 in 10 people)
- tiredness
- feeling sick
- increased blood levels of some enzymes of the liver (transaminases).

Common side effects (may affect up to 1 in 10 people):
- dizziness
- numbness or tingling of the mouth
- vomiting
- sleepiness
- increase in heart beat
- diarrhoea

- headache - abdominal pain - pain **Uncommon side effects** (may affect up to 1 in 100 people) - anaemia - allergic reactions - inflammation of the pancreas (pancreatitis). **Not known** (frequency cannot be estimated from the available data) - rash As riluzole oral suspension is more rapidly absorbed than riluzole tablets, a slight increase in tiredness, dizziness, diarrhoea and transaminases cannot be excluded. **Reporting of side effects** If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the the Spanish System of Farmacovigilance of Medicines for Human Use: https://www.notificaram.es. By communicating adverse effects you can help provide more information about the safety of this medicine.	
5. How to store TEGLUTIK Keep out of the sight and reach of children. Do not use TEGLUTIK after the expiry date which is stated on the carton and the bottle, after EXP. The expiry date refers to the last day of that month.	**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**

This medicinal product does not require any special storage conditions Once opened, use within 15 days. Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.	**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.**
6. Contents of the pack and other information **What TEGLUTIK contains** - The active substance is riluzole. 1 ml of oral suspension contains 5 mg of riluzole. - The other ingredients are: Liquid Sorbitol (E420), Aluminum magnesium Silicate, Xanthan Gum (E415), Saccharin Sodium (E954), Simethicone emulsion 30%, Sodium Laurilsulphate, Macrogol Cetostearyl Ether, Water. **What TEGLUTIK looks like and content of the pack** This medicine is presented as a slightly brown, opaque homogeneous oral suspension after being manually gently shaken. TEGLUTIK is available in a bottle of 250 and 300 ml with a plastic graduated oral dosing syringe. Pack sizes are: – cartoon box containing one or two bottles of 250 ml ofriluzole 5 mg/mL Oral Suspension – cartoon box containing one bottle of 300 mL of riluzole 5 mg/mL Oral Suspension. –	Each TIGLUTIK carton contains: 2 TIGLUTIK bottles 2 bottle adapters 2 10 mL oral syringes 2 syringe tip caps

The syringe barrel is graduated in milliliters up to 10 ml.	
Marketing Authorisation Holder ITALFARMACO S.A. San Rafael, 3 28108 Alcobendas (Madrid) Spain **Manufacturer** ITALFARMACO S.A. San Rafael, 28108 Alcobendas (Madrid) Spain	**Manufactured for:** ITF Pharma, Inc. 850 Cassatt Road, Suite 350 Berwyn, PA 19312 USA TIGLUTIK® is a licensed trademark of Italfarmaco S.A.

IMPORTED PRODUCT **SUMMARY OF PRODUCT CHARACTERISTICS (SMPC) (SPAIN)** **PRESCRIBING INFORMATION (ENGLISH TRANSLATION)**	**FDA-APPROVED PRODUCT** **PRESCRIBING INFORMATION (USPI) (U.S.)**
1. NAME OF THE MEDICINAL PRODUCT TEGLUTIK 5 mg/ml oral suspension	TIGLUTIK (riluzole) oral suspension
2. QUALITATIVE AND QUANTITATIVE COMPOSITION 1 ml of oral suspension contains 5 mg of riluzole Excipients with known effects: 1 ml of oral suspension contains 400 mg of sorbitol E420 (equivalent to 571.43 mg of liquid sorbitol (70%w/w). For a full list of excipients, see section 6.1.	**11. DESCRIPTION** TIGLUTIK (50 mg/10mL) oral suspension is a slightly brown, opaque, homogeneous suspension containing 50 mg of riluzole per 10 mL of suspension.
3. PHARMACEUTICAL FORM Oral suspension Slightly brown, opaque homogeneous suspension after being manually shaken.	**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.

4.1 Therapeutic indications TEGLUTIK is indicated to extend life or the time to mechanical ventilation for patients with amyotrophic lateral sclerosis (ALS). Clinical trials have demonstrated that riluzole extends survival for patients with ALS (see section 5.1). Survival was defined as patients who were alive, not intubated for mechanical ventilation and tracheotomy-free. There is no evidence that TEGLUTIK exerts a therapeutic effect on motor function, lung function, fasciculations, muscle strength and motor symptoms. TEGLUTIK has not been shown to be effective in the late stages of ALS. Safety and efficacy of TEGLUTIK has only been studied in ALS. Therefore, TEGLUTIK should not be used in patients with any other form of motor neurone disease.	**1. INDICATIONS AND USAGE** TIGLUTIK is indicated for the treatment of amyotrophic lateral sclerosis (ALS).
4.2 Posology and method of administration Treatment with TEGLUTIK should only be initiated by specialist physicians with experience in the management of motor neurone diseases. **Posology** The recommended daily dose in adults or elderly is 100 mg (50 mg every 12 hours). No significant increased benefit can be expected from higher daily doses. It is recommended to assume 10 ml two times a day of the suspension (i.e. 10 ml corresponds to 50 mg of Riluzole). Special populations *Paediatric population:* TEGLUTIK is not recommended for use in paediatric population, due to a lack of data on the safety and efficacy of riluzole in any neurodegenerative diseases occurring in children or adolescents. *Patients with impaired renal function:* TEGLUTIK is not recommended for use in patients with impaired renal function, as studies at repeated doses have not been conducted in this population (see section 4.4). *Older people:*	**2 DOSAGE AND ADMINISTRATION** **2.1 Dosage Information** The recommended dosage for TIGLUTIK is 50 mg (10 mL) taken orally or via Percutaneous Endoscopic Gastronomy tubes (PEG-tubes) 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)].* **2.2** Monitoring to Assess Safety Measure serum aminotransferases before and during treatment with TIGLUTIK [see Warnings and Precautions (5.1*)].* **8.USE IN SPECIFIC POPULATIONS** **8.4 Pediatric Use** Safety and effectiveness in pediatric patients have not been

Based on pharmacokinetic data, there are no special instructions for the use of TEGLUTIK in this population. Patients with impaired hepatic function: see section 4.3, section 4.4, and section 5.2. <u>Method of administration</u> The suspension can be given per oral administration and alternatively it is also suitable for administration via enteral feeding tubes. Dilution with liquids is not necessary. The suspension is administered by means of graduated dosing syringe. For instructions on handling of the product before administration, see section 6.6.	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)]*. **2.3 Important Administration Instructions** Gently shake the TIGLUTIK bottle for at least 30 seconds before administration. TIGLUTIK can be administered by mouth or via percutaneous

	endoscopic gastronomy tubes (PEG-tubes). Both silicone and polyurethane PEG tubes can be used. See the Instructions for Use for further administration details.

3. Contraindications Hypersensitivity to the active substance or to any of the excipients, listed in section 6.1. Hepatic disease or baseline transaminases greater than 3 times the upper limit of normal. Patients who are pregnant or breast-feeding.	**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)].

4.4 Special warnings and precautions for use Liver impairment: Riluzole should be prescribed with care in patients with a history of abnormal liver function, or in patients with slightly elevated serum transaminases (ALT/SGPT; AST/SGOT up to 3 times the upper limit of the normal range (ULN)), bilirubin and/or gamma-glutamyl transferase (GGT) levels. Baseline elevations of several liver function tests (especially elevated bilirubin) should preclude the use of riluzole (see section 4.8). Because of the risk of hepatitis, serum transaminases, including ALT, should be measured before and during therapy with riluzole. ALT should be measured every month during the first 3 months of treatment, every 3 months during the remainder of the first year, and periodically thereafter. ALT levels should be measured more frequently in patients who develop elevated ALT levels. Riluzole should be discontinued if the ALT levels increase to 5 times the ULN. There is no experience with dose reduction or rechallenge in patients who have developed an increase of ALT to 5 times ULN. Readministration of riluzole to patients in this situation cannot be recommended. Neutropenia: Patients should be warned to report any febrile illness to their physicians. The report of a febrile illness should prompt physicians to check white blood cell counts and to discontinue riluzole in case of neutropenia (see section 4.8). Interstitial lung disease	**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 mm3) within the first 2 months of riluzole treatment have been reported. Advise patients to report febrile illnesses.

Cases of interstitial lung disease have been reported in patients treated with riluzole, some of them were severe (see section 4.8). If respiratory symptoms develop such as dry cough and/or dysponea, chest radiography should be performed, and in case of findings suggestive of interstitial lung disease (e.g. bilateral diffuse lung opacities), riluzole should be discontinued immediately. In the majority of the reported cases, symptoms resolved after drug discontinuation and symptomatic treatment. <u>Renal impairment:</u> Studies at repeated doses have not been conducted in patients with impaired renal function (see section 4.2). This medicine contains 4000 mg sorbitol (E420) in 10 ml of oral suspension. The additive effect of concomitantly administered products containing sorbitol and dietary intake of sorbitol should be taken into account. The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly. Patients with hereditary problems of fructose intolerance should not take this medicine. This medicine contains less than 1 mmol sodium(23 mg) per 10 ml of oral suspension, that is to say essentially 'sodium-free'."	**5.3 Interstitial Lung Disease** TIGLUTIK can cause interstitial lung disease, including hypersensitivity pneumonitis. Discontinue TIGLUTIK immediately if interstitial lung disease develops.

4.5 Interaction with other medicinal products and other forms of interaction There have been no clinical studies to evaluate the interactions of riluzole with other medicinal products. In vitro studies using human liver microsomal preparations suggest that CYP 1A2 is the principal isozyme involved in the initial oxidative metabolism of riluzole. Inhibitors of CYP 1A2 (e.g. caffeine, diclofenac, diazepam, nicergoline, clomipramine, imipramine, fluvoxamine, phenacetin, theophylline, amitriptyline and quinolones) could potentially decrease the rate of riluzole elimination, while inducers of CYP 1A2 (e.g. cigarette smoke, charcoal-broiled food, rifampicin and omeprazole) could increase the rate of riluzole elimination.	**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)].

4.6 Fertility, pregnancy and lactation Pregnancy TEGLUTIK is contraindicated in pregnancy (see section 4.3 and 5.3). Clinical experience with riluzole in pregnant women is lacking. Breast-feeding TEGLUTIK is contraindicated in breast-feeding women (see section 4.3 and 5.3). It is not known whether riluzole is excreted in human milk. Fertility Fertility studies in rats revealed slight impairment of reproductive performance and fertility at doses of 15 mg/kg/day (which is higher than the therapeutic dose), probably due to sedation and lethargy.	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 There are no data on the presence of riluzole in human milk, the effects on the breastfed infant, or the effects on milk production. Riluzole or its metabolites have been detected in milk of lactating rat. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TIGLUTIK and any potential adverse effects on the breastfed infant from TIGLUTIK or from the underlying maternal condition. **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)].

4.7 Effects on ability to drive and use machines Patients should be warned about the potential for dizziness or vertigo, and advised not to drive or operate machinery if these symptoms occur. No studies on the effects on the ability to drive and use machines have been performed.	----------

4.8 Undesirable effects

Summary of safety profile

In phase III clinical studies conducted in ALS patients treated with riluzole, the most commonly reported adverse reactions were asthenia, nausea and abnormal liver function tests.

Tabulated summary of adverse reactions

Undesirable effects ranked under headings of frequency are listed below, using the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

	Very common	Common	Uncommon	Not known
Blood and lymphatic system disorders			Anaemia	Severe neutropenia (see section 4.4)
Immune system disorders			Anaphylactoid reaction, angioedema	
Nervous system disorders		Headache, dizziness, oral paraesthesia, somnolence		
Cardiac disorders		Tachycardia		
Respiratory, thoracic and mediastinal disorders			Interstitial lung disease (see section 4.4)	
Gastrointestinal disorders	Nausea	Diarrhoea, abdominal pain, vomiting	Pancreatitis	
Hepato-biliary disorders	Abnormal liver function tests			Hepatitis

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)]*

2.4 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.

Skin and subcutaneous tissue disorders				Rash
General disorders and administration site conditions	Asthenia	Pain		

Description of selected adverse reactions

Hepato-biliary disorders

Increased alanine aminotransferase usually appeared within 3 months after the start of therapy with riluzole; they were usually transient and levels returned to below twice the ULN after 2 to 6 months while treatment was continued. These increases could be associated with jaundice. In patients (n=20) from clinical studies with increases in ALT to more than 5 times the ULN, treatment was discontinued and the levels returned to less than 2 times the ULN within 2 to 4 months in most cases (see section 4.4).

Study data indicate that Asian patients may be more susceptible to liver function test abnormalities - 3.2% (194/5995) of Asian patients and 1.8% (100/5641) of Caucasian patients.

Riluzole oral suspension

Riluzole oral suspension and riluzole tablets total exposure was bioequivalent, while mean Cmax (the maximally achieved blood concentration of riluzole after ingestion) of the oral suspension was approximately 20% higher than mean Cmax of the riluzole tablets (see section 5.2).

There may be a slightly higher risk of the adverse events (e.g. dizziness, diarrhoea, asthenia and ALT increase) with the oral suspension.

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

Adverse Reaction	**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	3	2

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Sistema Español de Farmacovigilancia de Medicamentos de Uso Humano: www.notificaRAM.es

edema		
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.

6.2.1 Acute hepatitis and icteric toxic hepatitis *[see Warnings and Precautions (5.1)]*

6.2.2 Renal tubular impairment

4.9 Overdose Neurological and psychiatric symptoms, acute toxic encephalopathy with stupor, coma, and methemoglobinemia have been observed in isolated cases. In case of overdose, treatment is symptomatic and supportive.	**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.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other nervous system drugs, ATC code: N07XX02.

Mechanism of action

Although the pathogenesis of ALS is not completely elucidated, it is suggested that glutamate (the primary excitatory neurotransmitter in the central nervous system) plays a role for cell death in the disease.

Riluzole is proposed to act by inhibiting glutamate processes. The mode of action is unclear.

Clinical efficacy and safety

In a trial, 155 patients were randomised to riluzole 100 mg/day (50 mg twice daily) or placebo and were followed-up for 12 to 21 months. Survival, as defined in the second paragraph of section 4.1, was significantly extended for patients who received riluzole as compared to patients who received placebo. The median survival time was 17.7 months versus 14.9 months for riluzole and placebo, respectively.

In a dose-ranging trial, 959 patients with ALS were randomised to one of four treatment groups: riluzole 50, 100, 200 mg/day, or placebo and were followed-up for 18 months. In patients treated with riluzole 100 mg/day, survival was significantly higher compared to patients who received placebo. The effect of riluzole 50 mg/day was not statistically significant compared to placebo and the effect of 200 mg/day was essentially comparable to that of 100 mg/day. The median survival time approached 16.5 months versus 13.5 months for riluzole 100 mg/day and placebo, respectively.

In a parallel group study designed to assess the efficacy and safety of riluzole in patients at a late stage of the disease, survival time and motor function under riluzole did not differ significantly from that of placebo. In this study the majority of patients had a vital capacity less than 60%.

In a double-blind placebo-controlled trial designed to assess the efficacy and safety of riluzole in Japanese patients, 204 patients were randomised to riluzole 100 mg/day (50 mg twice daily) or placebo and were followed-up for 18 months. In this study, the efficacy was assessed on inability to walk alone, loss of upper limb function, tracheostomy, need for artificial ventilation, gastric tube feeding or death. Tracheostomy-free survival in patients treated with riluzole did not differ significantly from placebo. However, the power of this study to detect differences between treatment groups was low. Meta-analysis including this study and those described above showed a less striking effect on survival for riluzole as compared to placebo although the differences remained statistically significant.

12.CLINICAL PHARMACOLOGY

12.1Mechanism of Action

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

12.2Pharmacodynamics

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

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)].

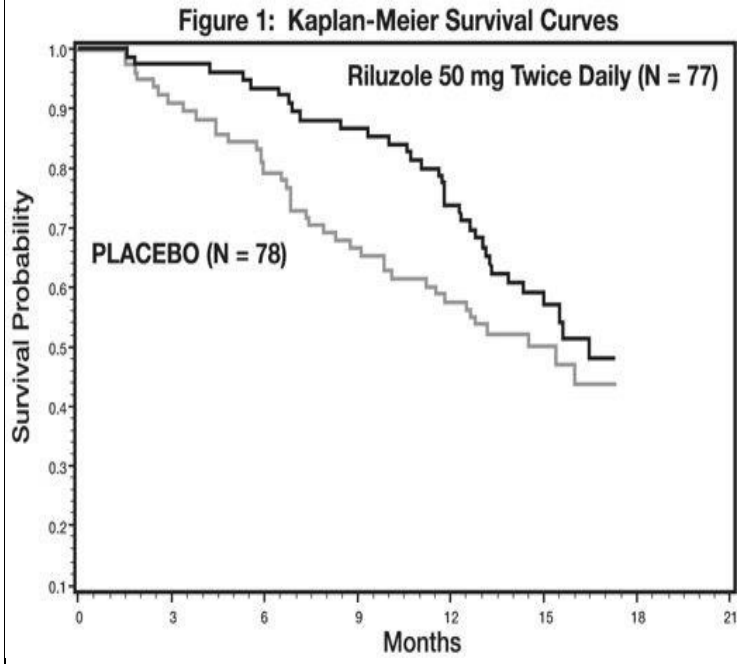
The efficacy of riluzole was demonstrated in two studies (Study 1 and 2) that evaluated 50 mg riluzole oral tablets twice daily in patients with amyotrophic lateral sclerosis (ALS). Both studies included patients with either familial or sporadic ALS, disease duration of less than 5 years, and baseline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

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

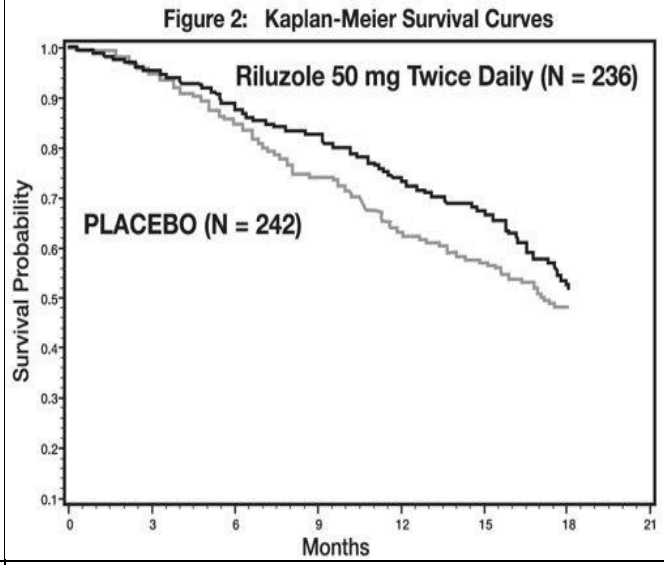


Study 2 was a randomized, double-blind, placebo-controlled

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) 
5.2 Pharmacokinetic properties The pharmacokinetics of riluzole have been evaluated in healthy male volunteers after single oral administration of 25 to 300 mg and after multiple-dose oral administration of 25 to 100 mg bid. Plasma levels increase linearly with the dose and the pharmacokinetic profile is dose-independent. With multiple dose administration (10 day-treatment at 50 mg riluzole bid), unchanged riluzole accumulates in plasma by about 2 fold and steady-state is reached in less than 5 days.	Pharmacokinetics A pharmacokinetic study in healthy adult subjects who received riluzole suspension 50 mg under fasting conditions demonstrated similar pharmacokinetics following intragastric administration via feeding tubes and oral administration.

Absorption

Riluzole is rapidly absorbed after oral administration with maximal plasma concentrations occurring within 60 to 90 minutes (Cmax = 173 ± 72 (sd) ng/ml). About 90% of the dose is absorbed and the absolute bioavailability is 60 ± 18%.

The rate and extent of absorption is reduced when riluzole is administered with high-fat meals (decrease in Cmax of 44%, decrease in AUC of 17%).

In a bioequivalence study the total exposure of riluzole 50 mg tablets and riluzole 5 mg/ml oral suspension were equivalent. (Ratio: 106.84%; 90% CI: 96.98-117.71%). Riluzole is more rapidly absorbed after the administration of oral suspension (Tmax approximately 30 minutes) with a Cmax approximately 20% higher than after the administration of riluzole tablets (Ratio: 122.32%; 90% CI: 103.28-144.88%). (see section 4.8).

Distribution

Riluzole is extensively distributed throughout the body and has been shown to cross the blood brain barrier. The volume of distribution of riluzole is about 245 ± 69 l (3.4 l/kg). Riluzole is about 97% protein bound and it binds mainly to serum albumin and to lipoproteins.

Biotransformation

Unchanged riluzole is the main component in plasma and is extensively metabolised by cytochrome P450 and subsequent glucuronidation. In vitro studies using human liver preparations demonstrated that cytochrome P450 1A2 is the principal isoenzyme involved in the metabolism of riluzole. The metabolites identified in urine are three phenolic derivatives, one ureido-derivative and unchanged riluzole.

Table 2 displays the pharmacokinetic parameters of riluzole.

Table 2. Pharmacokinetics of Riluzole[1]

Absorption	
Bioavailability (oral)	Approximately 60%
Dose	Linear over a dose range of 25 mg to 100 mg every 12 hours (1/2 to 2 times the recommended dosage)
Proportionality	AUC ↓ 9% and Cmax ↓ 55% (high fat meal)
Food effect[2]	0.8 hours
Time to peak plasma concentration (median)[2]	
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)

Specific Populations

Hepatic Impairment

Compared with healthy volunteers, the AUC of riluzole was approximately 1.7-fold greater in patients with mild chronic hepatic

The primary metabolic pathway for riluzole is initial oxidation by cytochrome P450 1A2 producing Nhydroxy-riluzole (RPR1 12512), the major active metabolite of riluzole. This metabolite is rapidly glucuronoconjugated to O- and N-glucuronides.

Elimination

The elimination half-life ranges from 9 to 15 hours. Riluzole is eliminated mainly in the urine.

The overall urinary excretion accounts for about 90% of the dose. Glucuronides accounted for more than 85% of the metabolites in the urine. Only 2% of a riluzole dose was recovered unchanged in the urine.

Special populations

Impaired renal function:

there is no significant difference in pharmacokinetic parameters between patients with moderate or severe chronic renal insufficiency (creatinine clearance between 10 and 50 ml.min-1) and healthy volunteers after a single oral dose of 50 mg riluzole.

Older people:

the pharmacokinetic parameters of riluzole after multiple dose administration (4.5 days of treatment at 50 mg riluzole bid) are not affected in the elderly (> 70 years).

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

Impaired hepatic function: the AUC of riluzole after a single oral dose of 50 mg increases by about 1.7 fold in patients with mild chronic liver insufficiency and by about 3 fold in patients with moderate chronic liver insufficiency. *Race:* a clinical study conducted to evaluate the pharmacokinetics of riluzole and its metabolite Nhydroxyriluzole following repeated oral administration twice daily for 8 days in 16 healthy Japanese and 16 Caucasian adult males showed in the Japanese group a lower exposure of riluzole (Cmcx 0.85 [90% CI 0.68-1.08] and AUC inf. 0.88 [90% CI 0.69-1.13]) and similar exposure to the metabolite. The clinical significance of these results is not known. *Gender*: a bioequivalence study has been conducted between TEGLUTIK° (oral suspension) and RILUTEK° (tablets). The results showed bioequivalence between both formulations in female subjects while a higher exposure in terms of Cmax and AUC of riluzole was observed in male subjects. However, no relevant clinical impact is expected.	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.
5.3 Precinical safety data Riluzole did not show any carcinogenicity potential in either rats or mice. Standard tests for genotoxicity performed with riluzole were negative. Tests on the major active metabolite of riluzole gave positive results in two in vitro tests. Intensive testing in	**13 NONCLINICAL TOXICOLOGY** **13.1Carcinogenesis, Mutagenesis, Impairment of Fertility** <u>Carcinogenesis</u> Riluzole was not carcinogenic in mice or rats when administered

seven other standard in vitro or in vivo assays did not show any genotoxic potential of the metabolite. On the basis of these data, and taking into consideration the negative studies on the carcinogenesis of riluzole in the mouse and rat, the genotoxic effect of this metabolite is not considered to be of relevance in humans. Reductions in red blood cell parameters and/or alterations in liver parameters were noted inconsistently in subacute and chronic toxicity studies in rats and monkeys. In dogs, haemolytic anaemia was observed. In a single toxicity study, the absence of corpora lutea was noted at a higher incidence in the ovary of treated compared to control female rats. This isolated finding was not noted in any other study or species. All these findings were noted at doses which were 2-10 times higher than the human dose of 100 mg/day. In the pregnant rat, the transfer of 14C- riluzole across the placenta to the foetus has been detected. In rats, riluzole decreased the pregnancy rate and the number of implantations at exposure levels at least twice the systemic exposure of humans given clinical therapy. No malformations were seen in animal reproductive studies. In lactating rats, 14C-riluzole was detected in milk.	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. <u>Mutagenesis</u> 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. <u>Impairment of Fertility</u> 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.

6.1 List of excipients Liquid Sorbitol (E420) Aluminium magnesium Silicate Xanthan Gum (E415) Saccharin Sodium (E954) Simethicone emulsion 30% Sodium Laurilsulphate Macrogol Cetostearyl Ether Water	**11. DESCRIPTION** 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.
6.3 Shelf life 3 years After the first opening: 15 days, without any special storage conditions	**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.
6.4 Special precautions for storage This medicinal product does not require any special storage conditions. For storage conditions after first opening of the medicinal product, see section 6.3	See before

6.5 Nature and contents of container Amber glass bottle equipped with a LDPE syringe-adapter and closed by means of a white-white HDPE child-proof screw cap. Pack sizes of one or two bottles of 250 ml of Riluzole 5 mg/mL Oral Suspension. Pack size of one bottle of 300 mL of Riluzole 5 mg/mL Oral Suspension. The bottle is packed with a plastic graduated oral dosing syringe. The syringe barrel is graduated in milliliters up to 10 ml. Not all pack sizes may be marketed.	**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

6.6 Special precautions for disposal and other handling Teglutik Oral Suspension is suitable for oral administration and alternatively it is also suitable for administration via enteral feeding tubes. **<u>Instruction for oral administration</u>** The suspension must be manually gently shaken for at least 30 seconds by rotating the bottle by 180° and the homogeneity should be visually verified. Open the bottle, connect the dosing syringe to the bottle syringe-adapter, invert the bottle and, by maintaining the bottle in the inverted position, slowly withdraw the suspension volume corresponding to the recommended dose (i.e. 10 ml corresponds to 50 mg of Riluzole). After the administration of the suspension, wash the syringe with tap water. **<u>Instructions for administration via enteral feeding tubes</u>** Teglutik Oral Suspension is suitable for use with enteral feeding tubes. The compatibility has been tested with tubes of silicone or polyurethane with diameters from 14Fr to 20 Fr. It is recommended to follow the instruction below: Ensure that the enteral feeding tube is free from obstruction before administration. 1. Flush the enteral tube with 30 ml of water 2. Administer the required dose of Teglutik oral suspension with a graduated dosing syringe 3. Flush the enteral tube with 30 ml of water.	**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.

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