COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Glentek 50 mg film-coated tablets (riluzole)

NL/H/4645/001/DC

Date: 2 March 2023

This module reflects the scientific discussion for the approval of Glentek 50 mg film-coated tablets. The procedure was finalised in the United Kingdom (UK/H/4433/001/DC). After a transfer in 2018, the current RMS is the Netherlands. The report presented below reflects the original procedure at the time of finalisation in the UK and has not been changed or updated since.

Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

GLENTEK 50MG FILM-COATED TABLETS

Procedure No: UK/H/4433/001/DC

UK Licence No: PL 25258/0105

Glenmark Generics (Europe) Limited

LAY SUMMARY

On 23 May 2012, Germany, Denmark, Spain, Finland, France, Ireland, Italy, the Netherlands, Sweden and the UK agreed to grant a Marketing Authorisation to Glenmark Generics (Europe) Limited for the medicinal product Glentek 50 mg film-coated tablets (PL 25258/0105; UK/H/4433/001/DC). The licence was granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After the national phase, a Marketing Authorisation was granted in the UK on 9 July 2012.

Glentek 50 mg film-coated tablets are 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. Glentek stops the release of glutamate and this may help in preventing the nerve cells being damaged.

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

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Glentek 50 mg film-coated tablets outweigh the risks; hence, a Marketing Authorisation was granted.

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Module 1

Product Name	Glentek 50 mg film-coated tablets
Type of Application	Generic, Article 10(1)
Active Substances	Riluzole
Form	Film-coated tablets
Strength	50 mg riluzole
MA Holder	Glenmark Generics (Europe) Limited, Laxmi House, 2 B Draycott Avenue, Kenton, Middlesex HA3 0BU, United Kingdom
Reference Member State (RMS)	UK
Concerned Member States (CMS)	Germany, Denmark, Spain, Finland, France, Ireland, Italy, the Netherlands and Sweden
Procedure Number	UK/H/4433/001/DC
Timetable	Day 210 – 23 May 2012

Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Glentek 50 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 50 mg of riluzole
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet
White to off-white, capsule shaped, bevelled edged film-coated tablets, engraved with '381' on one side and 'G' on other side

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Glentek is indicated to extend life or the time to mechanical ventilation for patients with amyotrophic lateral sclerosis (ALS).

Glentek is indicated in adults.

Clinical trials have demonstrated that Glentek 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 Glentek exerts a therapeutic effect on motor function, lung function, fasciculations, muscle strength and motor symptoms. Glentek has not been shown to be effective in the late stages of ALS.

Safety and efficacy of Glentek has only been studied in ALS. Therefore, Glentek should not be used in patients with any other form of motor neurone disease.

4.2 Posology and method of administration
Posology
Treatment with Glentek should only be initiated by specialist physicians with experience in the management of motor neurone diseases.

The recommended daily dose in adults or elderly is 100mg (50mg every 12 hours). No significant increased benefit can be expected from higher daily doses.

Special Population
Paediatric population
Glentek is not recommended for use in children, 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
Glentek 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).

Elderly
Based on pharmacokinetic data, there are no special instructions for the use of Glentek in this population.

Patients with impaired hepatic function
(See section 4.3, section 4.4, and section 5.2).

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients.

Hepatic disease or baseline transaminases greater than 3 times the upper limit of normal.

Patients who are pregnant or breast-feeding.

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

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 dyspnea, 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.

Renal impairment

Studies at repeated doses have not been conducted in patients with impaired renal function (see section 4.2).

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

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.

4.6 Pregnancy and lactation

Glentek is contraindicated (see section 4.3) in pregnancy (see section 5.3).
Clinical experience with riluzole in pregnant women is lacking.

Glentek is contraindicated (see section 4.3) in breast-feeding women (see section 5.3).
It is not known whether riluzole is excreted in human milk.

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

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. 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).

Blood and lymphatic system disorders
Uncommon: anaemia
Not known: severe neutropenia (see section 4.4)

Immune system disorders
Uncommon: anaphylactoid reaction, angioedema

Nervous system disorders
Common: headache, dizziness, oral paraesthesia and somnolence

Cardiac disorders
Common: tachycardia

Respiratory, thoracic and mediastinal disorders
Uncommon: interstitial lung disease (see section 4.4)

Gastrointestinal disorders
Very common: nausea
Common: diarrhoea, abdominal pain, vomiting
Uncommon: pancreatitis

Hepato-biliary disorders
Very common: abnormal liver function tests*. 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)
Not known: hepatitis

General disorders and administration site conditions
Very common: asthenia
Common: pain

* 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.

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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 trials

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.

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.

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%).

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.

Metabolism

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.

The primary metabolic pathway for riluzole is initial oxidation by cytochrome P450 1A2 producing N-hydroxy-riluzole (RPR112512), 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

Patients with 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.

Elderly: 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).

Patients with 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 N-hydroxyriluzole 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 (Cmax 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.

5.3 Preclinical 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 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.

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.

In the pregnant rat, the transfer of ^{14}C- 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, ^{14}C-riluzole was detected in milk.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
Calcium hydrogen phosphate anhydrous
Cellulose microcrystalline
Croscarmellose sodium
Silica colloidal anhydrous
Magnesium stearate

Coating:
Hypromellose
Titanium Dioxide (E171)
Macrogol 400

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
PVC/PVDC-Aluminium blisters in cartons of 28, 56, 98 film-coated tablets per carton.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Glenmark Generics (Europe) Limited
Laxmi House, 2 B Draycott Avenue,
Kenton, Middlesex HA3 0BU,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 25258/0105

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
09/07/2012

10 DATE OF REVISION OF THE TEXT
09/07/2012

Module 3

PACKAGE LEAFLET: INFORMATION FOR THE USER

Glentek 50 mg Film-coated Tablets
riluzole

Read all of this leaflet carefully before you start taking this medicine.
- 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. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT GLENTEK 50 MG FILM-COATED TABLETS ARE AND WHAT THEY ARE USED FOR

What Glentek 50 mg Film-coated Tablets are
The active substance in Glentek is riluzole which acts on the nervous system.

What Glentek 50 mg Film-coated Tablets are used for
Glentek 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. Glentek 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. BEFORE YOU TAKE GLENTEK 50 MG FILM-COATED TABLETS

Do not take Glentek 50 mg Film-coated Tablets
- if you are **allergic** (hypersensitive) to riluzole or any of the other ingredients of Glentek.
- if you have any **liver disease** or increased blood levels of some enzymes of the liver (transaminases).
- if you are **pregnant or breast-feeding**.

Take special care with Glentek 50 mg Film-coated Tablets
Tell your doctor:
- 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 you are less than 18 years of age. The use of Glentek is not recommended in children because there is no information available in this population.

If any of the above applies to you, or if you are not sure, tell your doctor who will decide what to do.

Taking other medicines
Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy and breast-feeding
You MUST NOT take Glentek if you are or 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 Glentek.

Driving and using machines
You can drive or use any tools or machines, unless you feel dizzy or light headed after taking this medicine.

3. HOW TO TAKE GLENTEK 50 MG FILM-COATED TABLETS

Always take Glentek exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.
The recommended dose is one tablet, twice a day.
The tablets should be taken by mouth, every 12 hours, at the same time of the day each day (e.g. in the morning and evening).

If you take more Glentek 50 mg Film-coated Tablets than you should
If you take too many tablets, contact your doctor or the nearest hospital emergency department immediately.

If you forget to take Glentek 50 mg Film-coated Tablets
If you forget to take your tablet, leave out that dose completely and take the next tablet at the usual time. Do not take a double dose to make up for a forgotten tablet.
If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

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

IMPORTANT

Tell your doctor immediately

- if you experience any **fever** (increase in temperature) because Glentek 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 this may be signs of **liver disease** (hepatitis). Your doctor may do regular blood tests while you are taking Glentek 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).

Very common side effects (affecting more than 1 in 10 patients) of Glentek are:

- tiredness
- feeling sick
- increased blood levels of some enzymes of the liver (transaminases).

Common side effects (affecting between 1 in 10 and 1 in 100 patients) of Glentek are:

- dizziness
- numbness or tingling of the mouth
- vomiting
- sleepiness
- increase in heart beat
- diarrhoea
- headache
- abdominal pain
- pain

Uncommon side effects (affecting between 1 in 100 and 1 in 1000 patients) of Glentek are:

- anaemia
- allergic reactions
- inflammation of the pancreas (pancreatitis).

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE GLENTEK 50 MG FILM-COATED TABLETS

Keep out of the reach and sight of children.

Do not use Glentek after the expiry date which is stated on the carton and the blister after EXP: the expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Glentek 50 mg Film-coated Tablets contain

The active substance is riluzole.

Each film-coated tablet contains 50 mg of riluzole.

The other ingredients are:

Core: Calcium hydrogen phosphate anhydrous, Cellulose microcrystalline, Croscarmellose sodium, Silica colloidal anhydrous, Magnesium stearate;

Coating: Hypromellose, Titanium Dioxide (E171), Macrogol-400.

What Glentek 50 mg Film-coated Tablets look like and content of the pack

Glentek 50 mg Film-coated Tablets are supplied as: White to off-white, capsule shaped, bevelled edged film-coated tablets, engraved with '381' on one side and 'G' on other side.

Glentek 50 mg Film-coated Tablets are available in PVC/PVDC aluminium blisters of 28, 56, 98 film-coated tablets.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder

Glenmark Generics (Europe) Limited
Laxmi House, 2 B Draycott Avenue,
Kenton, Middlesex HA3 0BU,
United Kingdom

Manufacturer

Glenmark Pharmaceuticals s.r.o.
Fibichova 143, 566 17 Vysoké Mýto,
Czech Republic

Glenmark Generics (Europe) Limited
The Old Sawmill, Hatfield Park,
Hatfield, Hertfordshire, AL9 5PG,
United Kingdom

This medicinal product is authorised in the Member States of the EEA under the following names:

Denmark :	Glentek
Finland :	Glentek 50 mg kalvopäällysteiset tabletit
France :	Glentek 50 mg, comprimé pelliculé
Germany :	Glentek 50 mg Filmtabletten
Ireland :	Glentek 50 mg Film-coated Tablets
Italy :	Glentek
Spain :	Glentek 50 mg comprimidos recubiertos con película
Sweden :	Glentek
The Netherlands :	Glentek 50 mg filmomhulde tabletten
The United Kingdom :	Glentek 50 mg Film-coated Tablets

This leaflet was last approved in 05/2012.

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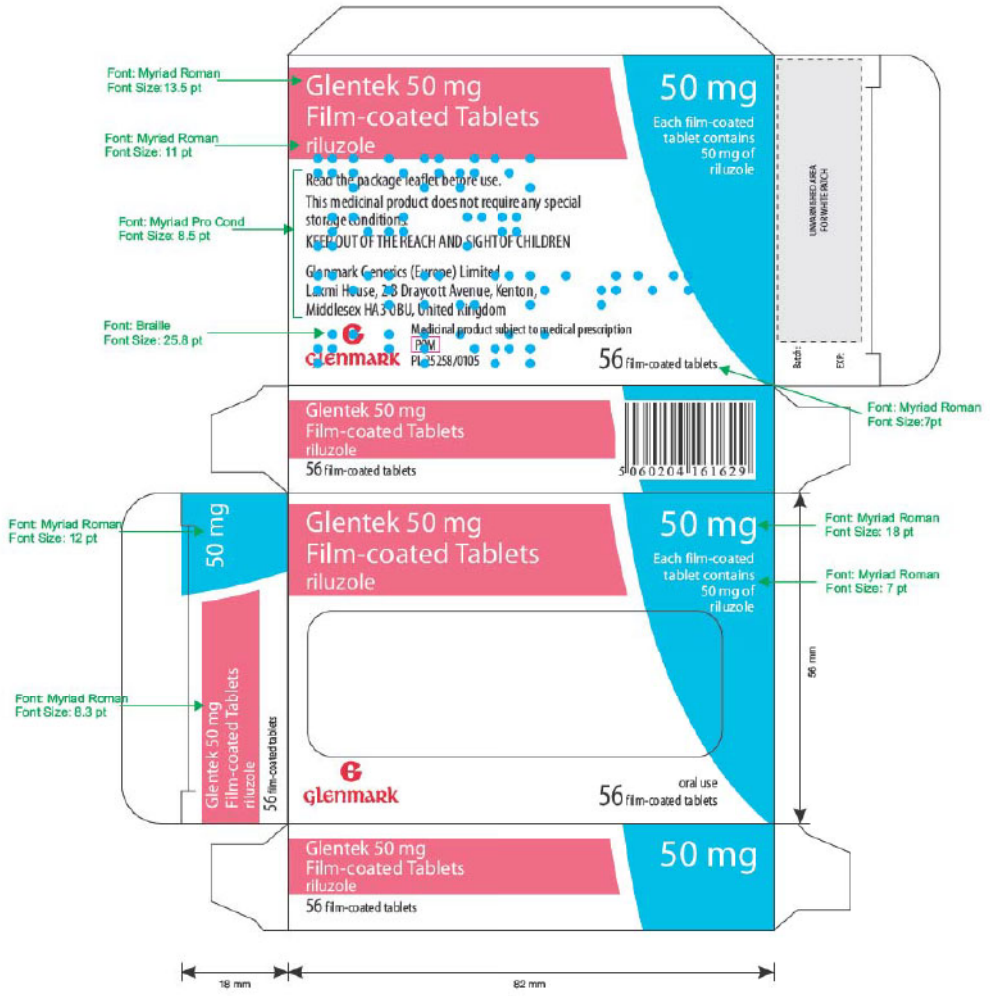
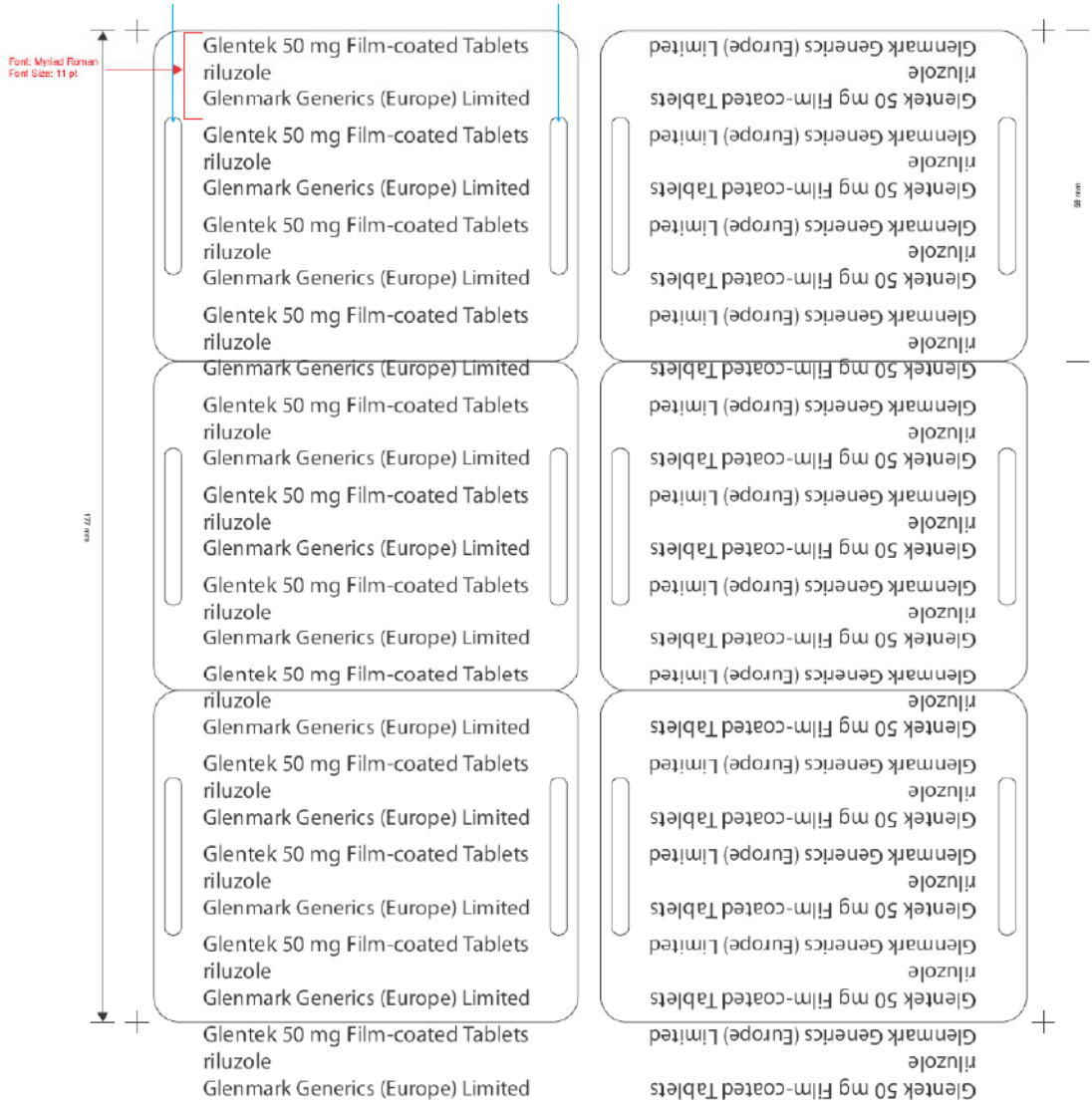
Module 4
Labelling

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Glentek 50 mg Film-coated Tablets
riluzole
Glenmark Generics (Europe) Limited
177 mm
98 mm

Module 5
Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the member states considered that the application for Glentek 50 mg film-coated tablets (PL 25258/0105; UK/H/4433/001/DC) could be approved. This application were submitted via the decentralised procedure, with the UK as reference member state (RMS), and Germany, Denmark, Spain, Finland, France, Ireland, Italy, the Netherlands and Sweden as concerned member states (CMS).

These are prescription-only medicines indicated to extend life or the time to mechanical ventilation for patients with amyotrophic lateral sclerosis (ALS).

This was an application made under the decentralised procedure (DCP), according to Article 10(1) of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product of Rilutek 50 mg film-coated tablets, which were initially granted to Aventis Pharma SA on the 10 June 1996.

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 and this may help in preventing the nerve cells being damaged. The mode of action is unclear.

No new non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

One bioequivalence study was performed, which compared the pharmacokinetics of Glentek 50 mg film-coated tablets (the test product) versus Rilutek 50 mg film-coated tablets (the reference product – Aventis Pharma SA, France). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice are in place for these product types at all sites responsible for the manufacture, assembly and batch release of this product.

The RMS and CMS considered that the application could be approved with the end of procedure (Day 210) on 23 May 2012. After a subsequent national phase, the licence was granted in the UK on 9 July 2012.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Glentek 50 mg film-coated tablets
Name(s) of the active substance(s) (INN)	Riluzole
Pharmacotherapeutic classification (ATC code)	Other nervous system drugs (N07XX02)
Pharmaceutical form and strength(s)	50 mg film-coated tablets
Reference numbers for the Mutual Recognition Procedure	UK/H/4433/001/DC
Reference Member State	United Kingdom
Member States concerned	Germany, Denmark, Spain, Finland, France, Ireland, Italy, the Netherlands and Sweden
Marketing Authorisation Number(s)	PL 25258/0105
Name and address of the authorisation holder	Glenmark Generics (Europe) Limited, Laxmi House, 2 B Draycott Avenue, Kenton, Middlesex HA3 0BU, United Kingdom

III SCIENTIFIC OVERVIEW AND DISCUSSION

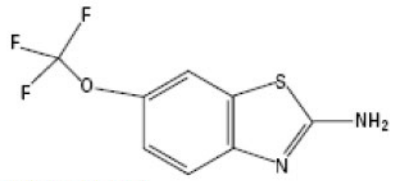
III.1 QUALITY ASPECTS

S. Active substance – Riluzole

rINN: Riluzole

Chemical name: 6-(trifluoromethoxy)-2-benzothiazolamine
2-amino-6-(trifluoromethoxy) benzothiazole

Structure:



Molecular formula: $C_8H_5F_3N_2OS$

Molecular weight: 234.20

Appearance: A white to pale yellow powder.

Solubility: Soluble in N, N-dimethylformamide, DMSO, methanol, dichloromethane; sparingly soluble in 0.1N HCl, very slightly soluble or insoluble in water and 0.1N NaOH.

Riluzole is not the subject of a European Pharmacopoeia monograph.

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Satisfactory certificates of analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

P. Medicinal Product

Other Ingredients

Other ingredients consist of the pharmaceutical excipients, calcium hydrogen phosphate anhydrous, cellulose microcrystalline, croscarmellose sodium, silica colloidal anhydrous, magnesium stearate, hypromellose, titanium dioxide (E171) and Macrogol 400.

All excipients comply with their respective European Pharmacopoeia monographs. Suitable batch analysis data have been provided for all excipients, showing compliance with their respective specifications.

None of the excipients are sourced from animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of this product.

Pharmaceutical Development
The objective of the development programme was to formulate a globally acceptable, stable and bioequivalent product that could be considered a generic medicinal product of the innovator product Rilutek 50 mg film-coated tablets (Aventis Pharma SA, France).

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution and impurity profiles have been provided for the proposed product and its respective innovator product.

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of the finished product. The manufacturing process has been validated and has shown satisfactory results. The marketing authorisation holder has committed to providing validation data for the first full-scale batches, as soon as these become available.

Finished Product Specification
The finished product specification proposed is acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications. Certificates of analysis have been provided for all working standards used.

Container-Closure System
The finished product is packaged in polyvinylchloride/polyvinylidene chloride-aluminium blisters, which are packed into cartons in pack sizes of 28, 56, 98 film-coated tablets per carton.

It has been stated that not all pack sizes may be marketed, however, the marketing authorisation holder has committed to submitting the mock-ups for any pack size to the relevant regulatory authorities for approval before marketing.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

Stability of the product
Stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years, with no specific storage conditions.

Bioequivalence/bioavailability
Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence study.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPC, PIL and labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ('user testing'), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Marketing Authorisation Application (MAA) form
The MAA form is pharmaceutically satisfactory.

Quality Overall Summary (Expert report)
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
The grant of a marketing authorisation is recommended.

III.2 NON-CLINICAL ASPECTS

As the pharmacodynamic, pharmacokinetic and toxicological properties of riluzole are well-known, no further non-clinical studies are required and none have been provided.

The applicant's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product's pharmacology and toxicology.

Suitable justification has been provided for the non-submission of an environmental risk assessment. As this product is intended for generic substitution with products that are currently marketed, no increase in environmental burden is expected.

There are no objections to the approval of this product from a non-clinical viewpoint.

III.3 CLINICAL ASPECTS

Pharmacokinetics
In support of this application, the marketing authorisation holder has submitted the following bioequivalence study:

An open-label, randomised, two-period, two-treatment, two-sequence, single-dose, crossover study to compare the pharmacokinetics of the test product Riluzole 50 mg film-coated tablets (Glenmark Generics Limited) versus the reference product Rilutek 50 mg film-coated tablets (Aventis Pharma SA, France) in healthy adult subjects under fasted conditions.

Volunteers were dosed with either treatment after an overnight fast of at least 10 hours. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 36 hours post dose. The two treatment arms were separated by a 7-day washout period.

The pharmacokinetic results (presented as geometric least-squares means, ratios and 90% confidence intervals) are presented below:

Parameters (Units)	In-transformed Data			90% Confidence Interval
	Geometric Least Squares Mean			
	Test Product-B	Reference Product-A	Ratio (B/A)%	
C_{max} (ng/mL)	175.39	187.65	93.47	83.99-104.02
AUC_{0-t} (ng.h/mL)	794.18	785.93	101.05	96.17-106.17
$AUC_{0-\infty}$ (ng.h/mL)	851.46	842.19	101.10	96.47-105.95

The 90% confidence intervals for C_{max} and AUC for test versus reference products are within predefined acceptance criteria. The data support the claim that the test product is bioequivalent to the reference product.

Efficacy
No new data on the efficacy have been submitted and none are required for this type of application.

Safety
With the exception of the data submitted during the bioequivalence study, no new safety data were submitted and none were required. No new or unexpected safety issues were raised by the bioequivalence data.

SmPC, PIL and Labels
The SmPC, PIL and labels are medically acceptable. The SmPC is consistent with that for the originator product.

Pharmacovigilance System and Risk Management Plan
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Suitable justification has been provided for not submitting a risk management plan for this product.

Clinical Expert Report
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Conclusion
The grant of a marketing authorisation is recommended.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of Glentek 50 mg film-coated tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit-risk balance.

NON-CLINICAL

No new non-clinical data were submitted and none are required for an application of this type.

CLINICAL

Bioequivalence has been demonstrated between the applicant's product and the reference product Rilutek 50 mg film-coated tablets (Aventis Pharma SA, France).

No new or unexpected safety concerns arose from this application.

The SmPC, PIL and labelling are satisfactory and consistent with those for the reference product.

BENEFIT-RISK ASSESSMENT

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's product and the originator product are interchangeable. Extensive clinical experience with riluzole is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is therefore considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome