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Sarizotan for respiratory symptoms associated Rett syndrome

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LAY SUMMARY

Rett syndrome (RTT) is a genetic disease that is caused by abnormalities in a gene called MECP2 which is important for the normal functioning of nerve cells. It is a rare disease which almost always affects females. Females with RTT lose their ability to properly control their muscles, have feeding difficulties and learning disabilities. Other symptoms include difficulty breathing, irregular heartbeat, sleeping problems, constipation, repetitive hand movements and fits.

Sarizotan is an oral medicinal product that is being developed for the treatment of respiratory symptoms associated with Rett syndrome. Sarizotan works by binding to serotonin and dopamine receptors. By stimulating serotonin and dopamine receptors, sarizotan replaces the effect of some of the missing serotonin in the brain and spinal cord. This is expected to help restore normal breathing rhythm in patients with Rett syndrome. Currently, there is no cure for Rett syndrome and treatment focuses on managing the symptoms. If licensed, sarizotan could become the first therapy approved for treatment of Rett Syndrome patients.

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TARGET GROUP

Respiratory symptoms associated with Rett's syndrome

TECHNOLOGY

DESCRIPTION

Sarizotan (EMD 128130) is a chromane derivative that exhibits affinity at serotonin and dopamine receptors.[1] Sarizotan is a serotonin (5-HT1A) receptor agonist and dopamine 2 (D2) receptor partial agonist and antagonist.[2] By stimulating these receptors, sarizotan replaces the effect of some of the missing serotonin in the brain and spinal cord. This is expected to help restore normal breathing rhythm in girls with Rett syndrome.[3] Sarizotan has been associated with a 70 to 85% reduction of apnoeas and hyperventilation episodes in preclinical testing with both acute and chronic dosing.[4]

In the phase III trial (NCT02790034), patients receive 2 to 10 mg (based on age and weight criteria) of sarizotan per day orally[5, 2]

Sarizotan does not currently have Marketing Authorisation in the EU for any indication.[6]

Sarizotan is in phase II/III clinical trials for dyskinesia in Parkinson's disease.[7]

INNOVATION and/or ADVANTAGES

Currently, there is no cure for Rett syndrome and treatment focuses on managing the symptoms.[8] If licensed, sarizotan could become the first therapy approved for treatment of Rett Syndrome patients.[9]

DEVELOPER

Newron Pharmaceuticals SPA (developer) in collaboration with Merck Serono/ Merck KGaA (originator)

REGULATORY INFORMATION/ MARKETING PLANS

Sarizotan received orphan drug designation for the treatment of Rett syndrome in the EU and the FDA in 2015.[3,9]

PATIENT GROUP

BACKGROUND

Rett syndrome (RTT) is a genetic disease that is caused by abnormalities in the methyl-Cp-G-binding protein 2 (MECP2) gene, which is important for the normal functioning of nerve cells. It almost exclusively affects females. Although the disease is genetic, most females affected (over 95%) do not inherit it from their parents. Females with RTT lose their ability to properly control their muscles, have feeding difficulties and learning disabilities. The features first start to appear between six and 18 months of age. Other symptoms include difficulty breathing, irregular heartbeat, sleeping problems, constipation, repetitive hand movements and seizures. RTT is a seriously debilitating and life-threatening disease mainly because of problems with breathing and the heart rhythm.[3]

Gastrointestinal problems, respiratory dysfunction such as hyperventilation, breath holding and apnoea, sleep disturbance, spinal curvature and epilepsy are common comorbidities. Studies show that lower respiratory tract infection is the most common cause of death.[10]

Other causes of death (one-quarter of deaths) are variations of sudden and unexplained death. The factors most strongly associated with an increased risk of sudden unexplained death in RTT are uncontrolled seizures, swallowing difficulties, and lack of mobility. Swallowing difficulties or poor oesophageal motility are suspected to increase the risk for aspiration pneumonia. The increased risk of death by pneumonia are compromised lung function due to scoliosis. Overall severity, seizures frequency and severity, immobility, and reduced weight are all risk factors. Death related to malnutrition is now rare in this country.[11]

CLINICAL NEED and BURDEN OF DISEASE

RTT is a rare neurological disorder affecting primarily females due to the mutation of the MECP2 gene.[3, 8] It affects females with approximately 15,000 patients in the US and 20,000 in the EU, with an incidence of 1 out of 10,000 to 15,000 live female births.[12]

According to studies the likelihood of survival is 77.6% at 20 years, 71.5% at 25 years and 59.8% at 37 years.[10]

According to the Hospitals Episode Statistics (HES) in 2016-17, there were 90 finished consultant episodes (FCEs), 80 admissions, 701 FCE bed days, and 24 day cases due to Rett syndrome (ICD-10 code: F84.2).[13] This however does not represent all patients with respiratory symptoms.

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

No relevant guidance identified.

NHS ENGLAND and POLICY GUIDANCE

No relevant guidance identified.

OTHER GUIDANCE

Rett syndrome. Management & Care Guidelines. 2013.[14]

CURRENT TREATMENT OPTIONS

Currently there are no authorised treatments were available for Rett syndrome.[8] Girls with the disease are given physiotherapy, speech therapy and nutritional support to help relieve the symptoms of the disease. Medicines to control seizures are also used, as well as laxatives and painkillers.[3]

EFFICACY and SAFETY

Trial	NCT02790034, Sarizotan/001/II/2015; 4 years and older; sarizotan vs placebo; phase II/III
Sponsor	Newron Pharmaceuticals SPA
Status	Ongoing
Source of Information	Trial registry[5]
Location	EU (Italy, UK), USA, Australia and India
Design	Randomised, placebo-controlled, parallel assignment, double-blind
Participants	n=129 (planned); aged 4 years and older; males and females, respiratory symptoms associated with Rett syndrome
Schedule	Subjects patients receive 2 to 10 mg (based on age and weight criteria) of sarizotan per day orally
Follow-up	Follow-up: 24 weeks
Primary Outcomes	• Reduction in respiratory abnormality in patients with Rett syndrome [Time frame: 3 days prior to baseline up to week 24]
Secondary Outcomes	• Efficacy of sarizotan assessed by the caregiver [Time frame: 24 weeks] • Safety and tolerability of sarizotan in patients with Rett syndrome with respiratory symptoms. [Time frame: 24 weeks] • Respiratory symptoms - Percent time spent with breathing dysrhythmia per hour [Time Frame: 24 weeks] • Respiratory symptoms - Number of hyperventilation episodes [Time frame: 24 weeks] • Respiratory symptoms - Oxygen saturation [Time frame: 24 weeks] • Respiratory symptoms - Respiratory Distress Index; [Time frame: 24 weeks] • Respiratory symptoms - Incidence of breathing dysrhythmia episodes [Time frame: 24 weeks] • Motor behaviour [Time frame: 24 weeks] • Global change from baseline [Time frame: 24 weeks] • Caregiver burden [Time Frame: 24 weeks] • Overall assessment of symptoms of Rett syndrome [Time frame: 24 weeks] • Pharmacokinetics profile of sarizotan and its comparison with the profile in adults [Time frame: Baseline, 1 and 4 hr post-dose on day 1, and 1 and 4 hr post-dose on day 15]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Primary completion date reported as July 2018.

ESTIMATED COST and IMPACT

COST

The cost of Sarizotan is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☐ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☐ Other

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☒ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other

☐ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs

☐ Other reduction in costs

☐ Other: *specify, e.g. uncertain unit cost compared to existing treatments*

☒ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified: *specify*

☒ None identified

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