# Report EVRYSDI® Risdiplam

| Product & Mechanism of action | Authorized indications Licensing status | Essential therapeutic features | NHS impact |
|---|---|---|---|
| **Substance:** Risdiplam<br><br>**Brand Name:** Evrysdi ™<br><br>**Originator/licensee:** Roche Registration GmbH<br><br>**Classification:** NCE<br><br>**ATC code:** M09AX10<br><br>**Orphan Status:**<br>**Eu:** Yes<br>**Us:** Yes<br><br>**Mechanism of action:** Risdiplam is a SMN2 splicing modifier designed to treat pts with SMA caused by mutations in chromosome 5q that lead to SMN protein deficiency. Risdiplam was shown to increase exon 7 inclusion in SMN2 mRNA transcripts and production of full-length SMN protein in the brain [1].<br>---<br>**References:**<br>**1.**https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/213535Orig1s000SumR.pdf<br>**2**.https://www.ema.europa.eu/en<br>**3.**https://www.fda.gov/<br>**4.**https://clinicaltrials.gov/<br>**5.**https://www.drugs.com/price-guide/evrysdi<br>**6.**http://www.io.nihr.ac.uk/wp-content/uploads/2019/06/13205-Risdiplam-for-Spinal-Muscular-Atrophy-V1.0-MAY2019-NON-CONF.pdf | **Authorized Indication:**<br>**EMA:** Risdiplam is indicated for the treatment of 5q SMA in pts ≥2 months of age, with a clinical diagnosis of SMA Type 1, Type 2 or Type 3 or with one to four SMN2 copies [2].<br><br>**FDA**: Risdiplam is indicated for the treatment of SMA in pts ≥2 months of age [3].<br><br>**Route of administration:** OS<br><br>**Licensing status**<br>**EU CHMP P.O. date:** 25/02/2021<br>**FDA M.A. date:** 08/07/2020<br><br>**EU Speed Approval Pathway:** Yes<br>**FDA Speed Approval Pathway:** Yes<br><br>---<br>**ABBREVIATIONS:**<br>**AUC024$_{h,ss}$:** Area under the plasma concentration-time curve within time span 0 to 24 hours, at the steady state.<br>**BSID-III**: Bayley scales of infant and toddler development third edition<br>**CHMP:** Committee for Medicinal Products for Human Use<br>**IV:**intravenous<br>**M.A.:** Marketing Authorization<br>**MFM32**: Motor Function Measure 32<br>**O.S.:** oral administration<br>**PD:** pharmacodynamics<br>**PK:** pharmacokinetics<br>**P.O.:** Positive Opinion<br>**Pts**: patients<br>**SAEs**: serious adverse events<br>**SMA:** spinal muscular atrophy<br>**SMN2:** survival of motor neuron | **Summary of clinical EFFICACY:**<br>**Study BP39056 (FIREFISH, NCT02913482):** phase II/III open-label, two-part seamless, multi-center which included 62 infant pts with Type 1 (infantile-onset) SMA aged 1-7 months at enrollment.<br>Part one (n=21): the primary objective of this part was to evaluate the safety, tolerability, PK, and PD of risdiplam, and to select the dose for part two. This part of the study included two cohorts. In cohort one (n=4) pts were administered with a "dose-escalation", while in cohort two (high-dose cohort; n=17) pts were dosed to achieve a target mean AUC024$_{h,ss}$≤ 2000 ng x h/mL. The primary endpoint was to establish the recommended part two dose of risdiplam. Based on the concentration of risdiplam in the blood, an increase in SMN protein and safety, the higher dose of risdiplam was chosen to be studied further in part 2. The higher dose of risdiplam also had more promising effects on the motor function of the pts in the trial, as well as on swallowing and feeding (clinical efficacy data for pts in this part of the study indicated that 33% [7/21] of all pts treated with risdiplam, and 41% [7/17] of pts treated in the high-dose cohort, achieved sitting without support for five seconds or more after 12 months of risdiplam treatment. Moreover, after a minimum of 23 months of treatment with risdiplam, 81% [17/21] of pts were older than 28 months and alive without permanent ventilation) [1].<br>Part two (n=41): The primary endpoint was the percentage of infants who were sitting without support at 12-months of treatment assessed by the gross motor scale of the BSID-III. Topline results of this part showed that 29% of the pts were able to sit without support for five seconds and 85% were alive while not requiring permanent ventilation after 12 months of treatment with risdiplam [1] [4].<br><br>**Study BP39055 (SUNFISH, NCT02908685):** BP39055 was a phase II/III, two-part multinational, randomized, double-blind, placebo-controlled, study of risdiplam in subjects with Type 2 or 3 SMA aged 2-25 years at enrollment.<br>Part one (N=51): the main objective was to evaluate the safety, tolerability, PK, and PD of risdiplam, and to select the dose for part two of the study. This part also included assessments of motor and respiratory function, and an open-label extension. The primary endpoint was to assess the recommended part two dose of risdiplam.<br>Part two (N=180): this part enrolled 180 non-ambulatory pts (128 [71%] with Type 2, and 52 [29%] with Type 3 SMA). The objective was to evaluate the efficacy of risdiplam, compared with placebo, in terms of motor function in pts with Type 2 SMA and non-ambulatory Type 3 SMA. The primary efficacy endpoint for this phase was the change from baseline in the MFM32* at month 12. Pts treated with risdiplam showed a mean 1.4-point increase on the MFM32 after 12 months of treatment, while pts on placebo experienced a mean 0.2-point decrease (p=0.016) [1] [4].<br><br>**Summary of clinical SAFETY:**<br>The most frequent SAEs with a greater incidence in the risdiplam arm than on placebo arm were mainly upper respiratory tract infections (32%), pyrexia (21%), headache (20%), diarrhea (17%), rash (13%), constipation and arthralgias. There were no deaths in the SUNFISH study, whilst six people with Type 1 SMA died in the FIREFISH study. Deaths were related to respiratory complications of SMA and unlikely causally related to risdiplam. *In vitro* and *in vivo* studies reported concerning safety signals for retinal toxicity and epithelial cell reactions, however extensive ophthalmological monitoring in the clinical studies did not show clinical signals for retinal toxicity. Overall, the safety profile of risdiplam resulted acceptable for the indication[1].<br><br>**Ongoing studies:**<br>● ***For the same indication:***Yes<br>● ***For other indications:*** No<br>[Phase III, but if it is an O/OE drug, also Phase II]<br><br>**Discontinued studies (for the same indication):** No | **Cost of therapy:**<br>The cost for risdiplam oral powder for reconstitution (0.75 mg/mL) is around $11,671 for a supply of 80 milliliters ($145.89 per unit) [5].<br>*The estimated cost for a 1-month therapy is around $28,333.*<br><br>**Epidemiology:**<br>Based on a 2019 European study data on prevalence and incidence of rare diseases, the incidence of proximal SMA type I, II, III and IV is estimated to be 0.26, 1.23, 1.1 and 0.32 per 100,000 respectively [6].<br><br>**POSSIBLE PLACE IN THERAPY**<br>Risdiplam will be the first oral drug approved for the treatment of SMA. Currently, two drugs for the treatment of SMA are available: nusinersen (Spinraza, intrathecal injection) and onasemnogeneabeparvovec (Zolgensma, solution for IV infusion). However, some pts are not able to receive nusinersen due to limitations with intrathecal administration and some pts are not eligible to receive onasemnogeneabeparvovec due to age (approved for pts < 2 years) [1] [6].<br><br>**OTHER INDICATIONS IN DEVELOPMENT:**<br>No<br><br>**SAME INDICATION IN EARLIER LINE(S) OF TREATMENT:** No<br><br>**OTHER DRUGS IN DEVELOPMENT for the SAME INDICATION**<br>[if it is..]Yes (branaplam)<br><br>*Service reorganization: Yes<br>*Possible off label use: No |

*The MFM 32 is an ordinal scale constructed for use in pts with neuromuscular disorders. The scale comprises 32 items that evaluate physical function. The 32 scores are summed to yield a total score expressed as the percentage of the maximum possible score (the one obtained with no physical impairment); the lower the total score, the more severe the impairment.