יוני 2024

EVRYSDI® (Risdiplam 0.75mg/ml)

אוורִיסדי

Powder for oral solution

רופא/ה יקר/ה, רוקח/ת יקר/ה,

חברת רוש פרמצבטיקה (ישראל) בע"מ מבקשת להודיעכם על הרחבת התוויה לתכשיר אוורִיסדי **מגיל לידה**.

ההתוויה שאושרה לתכשיר בישראל:

EVRYSDI is indicated for the treatment of spinal muscular atrophy (SMA) types 1, 2 and 3 **in pediatric and adult patients**

המינון של התכשיר אוורִיסדי תלוי בגיל ובמשקל המטופלים:

Age and body weight	***Recommended daily dose***
< 2 months of age	**0.15 mg/kg**
2 months to < 2 years of age	0.20 mg/kg
⩾ 2 years of age (< 20 kg)	0.25 mg/kg
⩾ 2 years of age (⩾ 20 kg)	5 mg

יש ליטול אוורִיסדי פעם אחת ביום לאחר ארוחה

הסבר:

<u>טקסט עם קו תחתי</u> מציין טקסט שהוסף לעלון.

~~טקסט עם קו חוצה~~ מציין טקסט שהוסר מן העלון.

למידע נוסף יש לעיין בעלון לרופא ובעלון לצרכן כפי שאושרו ע"י משרד הבריאות.

העלונים המעודכנים נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות, וניתן לקבלם מודפסים על-ידי פנייה לבעל הרישום: רוש פרמצבטיקה (ישראל) בע"מ, ת.ד 6391 , הוד השרון 4524079 טלפון 09-9737777. כתובתנו באינטרנט: www.roche.co.il.

ב ב ר כ ה,

בתאור צפרי חגג
מחלקת רישום

לילי אדר
רוקחת ממונה

4.1 Therapeutic indications

EVRYSDI is indicated for the treatment of spinal muscular atrophy (SMA) types 1, 2 and 3 in ~~patients 2 months of age and older~~ pediatric and adult patients

4.2 Posology and method of administration

Treatment with Evrysdi should be initiated by a physician with experience in the management of SMA.

Posology

The recommended once daily dose of Evrysdi is determined by age and body weight (see Table 1). Evrysdi is taken orally once a day after a meal at approximately the same time each day.

Table 1. Dosing regimen by age and body weight

Age and body weight	***Recommended daily dose***
< 2 months of age	0.15 mg/kg
2 months to < 2 years of age	0.20 mg/kg
⩾ 2 years of age (< 20 kg)	0.25 mg/kg
⩾ 2 years of age (⩾ 20 kg)	5 mg

Treatment with a daily dose above 5 mg has not been studied.

[…]

Paediatric population
~~Evrysdi is not indicated for infants under 2 months of age.~~
~~The safety and efficacy of risdiplam in paediatric patients < 2 months of age have not yet been established (see section 5.1). No data are available.~~
Use of Evrysdi for SMA in patients 2 months of age and younger is supported by pharmacokinetic and safety data from paediatric patients 16 days and older (see sections 4.8, 5.1 and 5.2), and pharmacokinetic modeling and simulation to identify the dosing regimen. No data on risdiplam pharmacokinetics are available in patients less than 16 days of age

Method of administration

[…]

Selection of the oral syringe for the prescribed daily dose:

Syringe size	*Dosing volume*	*Syringe markings*
1 mL	0.3 mL to 1 mL	0.01 mL
6 mL	1 mL to 6 mL	0.1 mL
12 mL	6.2 mL to 6.6 mL	0.2 mL

For the calculation of dosing volume, the syringe markings need to be considered. The dose volume should be rounded to the nearest graduation mark on the selected oral syringe.

[…]

4.8 Undesirable effects

Summary of the safety profile

In infantile-onset SMA patients, the most common adverse reactions observed in Evrysdi clinical studies were pyrexia (54.8%), rash (29.0%) and diarrhoea (19.4%).

In later-onset SMA patients, the most common adverse reactions observed in Evrysdi clinical studies were pyrexia (21.7%), headache (20.0%), diarrhoea (16.7%), and rash (16.7%).

The adverse reactions listed above occurred without an identifiable clinical or time pattern and generally resolved despite ongoing treatment in infantile-onset and later-onset SMA patients.

Based on the primary analysis of RAINBOWFISH, the safety profile of Evrysdi in pre-symptomatic patients is consistent with the safety profile of symptomatic infantile-onset and later-onset SMA patients. The RAINBOWFISH study enrolled 26 patients with pre-symptomatic SMA between 16 and 41 days of age at the time of the first dose (weight range 3.1 to 5.7 kg). The median exposure duration was 20.4 months (range: 10.6 to 41.9 months). Limited post-marketing data are available in neonates <20 days of age.

See also section 5.3 for the effects of Evrysdi observed in nonclinical studies.

[…]

5.1 Pharmacodynamic properties

[…]
Clinical efficacy and safety

The efficacy of Evrysdi for the treatment of SMA patients with infantile-onset (SMA Type 1) and later-onset SMA (SMA type 2 and 3) was evaluated in 2 pivotal clinical studies, FIREFISH and SUNFISH. Efficacy data of Evrysdi for the treatment of pre-symptomatic SMA patients was evaluated in the RAINBOWFISH clinical study.
Patients with a clinical diagnosis of Type 4 SMA have not been studied in clinical trials.

[…]

Pre-symptomatic SMA (RAINBOWFISH)

Study BN40703 (RAINBOWFISH) is an open-label, single-arm, multicenter clinical study to investigate the efficacy, safety, pharmacokinetics, and pharmacodynamics of

Evrysdi in infants from birth to 6 weeks of age (at first dose) who have been genetically diagnosed with SMA but do not yet present with symptoms.

The efficacy in pre-symptomatic SMA patients was evaluated at Month 12 in 26 patients [intent-to-treat (ITT) population] treated with Evrysdi: eight patients, 13 patients, and 5 patients had 2, 3, and ≥4 copies of the *SMN2* gene, respectively. The median age of these patients at first dose was 25 days (range: 16 to 41 days), 62% were female, and 85% were Caucasian. At baseline, the median CHOP-INTEND score was 51.5 (range: 35.0 to 62.0), the median HINE-2 score was 2.5 (range: 0 to 6.0), and the median ulnar nerve compound muscle action potential (CMAP) amplitude was 3.6 mV (range: 0.5 to 6.7 mV).

The primary efficacy population (N=5) included patients with 2 *SMN2* copies and a baseline CMAP amplitude ≥ 1.5 mV. In these patients, the median CHOP-INTEND score was 48.0 (range: 36.0 to 52.0), the median HINE-2 score was 2.0 (range 1.0 to 3.0), and the median CMAP amplitude was 2.6 mV (range: 1.6 to 3.8 mV) at baseline.

The primary endpoint was the proportion of patients in the primary efficacy population with the ability to sit without support for at least 5 seconds (BSID-III gross motor scale, Item 22) at Month 12; a statistically significant and clinically meaningful proportion of patients achieved this milestone compared to the predefined performance criterion of 5%.

The key efficacy endpoints of Evrysdi treated patients are shown in Table 5 and 6, and in Figure 5.

Table 5. Sitting ability as defined by BSID-III Item 22 for pre-symptomatic patients at Month 12

Efficacy Endpoint	**Population**		
	Primary Efficacy (N=5)	Patients with 2 *SMN2* copies[a] (N=8)	ITT (N=26)
Proportion of patients sitting without support for at least 5 seconds (BSID-III, Item 22); (90% CI)	80% (34.3%, 99.0%) $p < 0.0001$[b]	87.5% (52.9%, 99.4%)	96.2% (83.0%, 99.8%)

Abbreviations: BSID-III = Bayley Scales of Infant and Toddler Development – Third Edition; CI=Confidence Interval; ITT=Intent-to-treat.
[a] Patients with 2 *SMN2* copies had a median CMAP amplitude of 2.0 (range 0.5 – 3.8) at baseline.
[b] p-value is based on a one-sided exact binomial test. The result is compared to a threshold of 5%.

Additionally, 80% (4/5) of the primary efficacy population, 87.5% (7/8) of patients with 2 *SMN2* copies, and 80.8% (21/26) of patients in the ITT population achieved sitting without support for 30 seconds (BSID-III, Item 26).

Patients in the ITT population also achieved motor milestones as measured by the HINE-2 at Month 12 (N=25). In this population 96.0% of patients could sit [1 patient (1/8 patients with 2 *SMN2* copies) achieved stable sit and 23 patients (6/8, 13/13, 4/4 of patients with 2, 3, and ≥4 *SMN2* copies, respectively) could pivot/rotate]. In addition, 84% of patients could stand; 32% (N=8) patients could stand with support (3/8, 3/13 and 2/4 patients with 2, 3, and ≥4 *SMN2* copies, respectively) and 52% (N=13) patients could stand unaided (1/8, 10/13 and 2/4 of patients with 2, 3, and ≥4 *SMN2* copies, respectively). Furthermore, 72% of patients could bounce, cruise or walk; 8% (N=2) patients could bounce (2/8 patients with 2 *SMN2* copies), 16% (N=4) could cruise (3/13 and 1/4 patients with 3 and ≥4 *SMN2* copies, respectively) and 48% (N=12) could walk

independently (1/8, 9/13 and 2/4 patients with 2, 3, and ≥4 *SMN2* copies, respectively). Seven patients were not tested for walking at Month 12.

Table 6. Summary of key efficacy endpoints for pre-symptomatic patients at Month 12

Efficacy Endpoints	ITT population (N=26)
Motor Function	
Proportion of patients who achieve a Total score of 50 or higher in the CHOP-INTEND (90 CI%)	92%[a] (76.9%, 98.6%)
Proportion of patients who achieve a Total score of 60 or higher in the CHOP-INTEND (90 CI%)	80%[a] (62.5%, 91.8%)
Feeding	
Proportion of patients with the ability to feed orally (90 CI%)	96.2%[b] (83.0%, 99.8%)
Healthcare Utilization	
Proportion of patients with no hospitalisations[c] (90 CI%)	92.3% (77.7%, 98.6%)
Event-Free Survival[d]	
Proportion of patients with Event-Free Survival (90 CI%)	100% (100%, 100%)

Abbreviations: CHOP-INTEND=Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CI=Confidence Interval

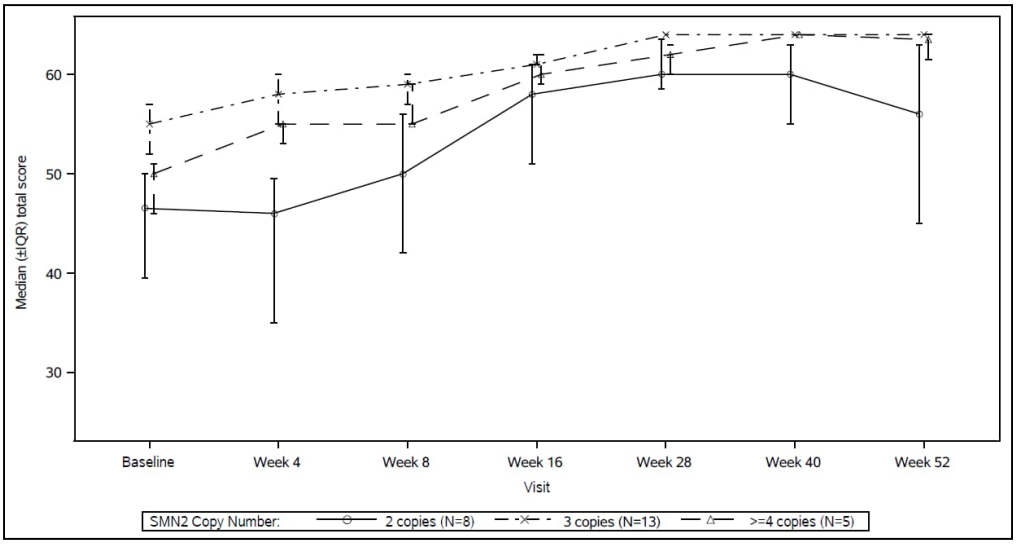
[a] Based on N=25

[b] One patient was not assessed.

[c] Hospitalisations include all hospital admissions which spanned at least two days, and which are not due to study requirements.

[d] An event refers to death or permanent ventilation; permanent ventilation is defined as tracheostomy or ≥16 hours of non-invasive ventilation per day or intubation for > 21 consecutive days in the absence of, or following the resolution of, an acute reversible event.

Figure 5. Median Total CHOP-INTEND Scores by Visit and *SMN2* copy number (ITT population)



Abbreviations: IQR = Interquartile range; SMN2 = Survival of Motor Neuron 2.

5.2 Pharmacokinetic properties

Pharmacokinetic parameters have been characterised in healthy adult subjects and in patients with SMA.

After administration of treatment as an oral solution, PK of risdiplam were approximately linear between 0.6 and 18 mg. Risdiplam's PK was best described by a population PK model with three-transit-compartment absorption, two-compartment disposition and first-order elimination. Body weight and age were found to have significant effect on the PK.

The estimated exposure (mean $AUC_{0\text{-}24h}$) for infantile-onset SMA patients (age 2-7 months at enrolment) at the therapeutic dose of 0.2 mg/kg once daily was 1930 ng.h/mL. The estimated mean exposure in pre-symptomatic infants (16 days to <2 months of age) in the RAINBOWFISH study was 2020 ng.h/mL at 0.15 mg/kg after 2 weeks once daily administration. The estimated exposure for later-onset SMA patients (2-25 years old at enrolment) in the SUNFISH (Part 2) study at the therapeutic dose (0.25 mg/kg once daily for patients with a body weight <20 kg; 5 mg once daily for patients with a body weight ≥20 kg) was 2070 ng.h/mL. The estimated exposure (mean $AUC_{0\text{-}24h}$) for SMA treatment non-naïve patients (age 1-60 years at enrolment) was 1700 ng.h/mL at the therapeutic dose of 0.25 mg/kg or 5 mg. The observed maximum concentration (mean C_{max}) was 194 ng/mL at 0.2 mg/kg in FIREFISH, 120 ng/mL in SUNFISH Part 2 , ~~and~~ 129 ng/mL in JEWELFISH, and the estimated maximum concentration at 0.15 mg/kg in RAINBOWFISH is 111 ng/mL.

[…]

Pharmacokinetics in special populations

Paediatric population
Body weight and age were identified as covariates in the population PK analysis. ~~The~~On the basis of such model, the dose is therefore adjusted based on age (below and above 2 months and 2 years) and body weight (up to 20 kg) to obtain similar exposure across the age and body weight range. Limited PK ~~No~~ data are available in patients less than 20 days ~~2 months~~ of age~~.~~ , since only one 16-day-old neonate received risdiplam at a lower dose (0.04 mg/kg) in clinical studies.

No data on risdiplam pharmacokinetics are available in patients less than 16 days of age

[…]

6.5 Nature and contents of container

Amber type III glass bottle with a tamper-evident child resistant screw cap.

Each carton contains; one bottle, 1 press-in bottle adaptor, two re-usable 1 mL, two re-usable 6 mL and ~~two~~ one re-usable 12 mL graduated amber oral syringes.

עדכונים מהותיים בעלון לצרכן

1. למה מיועדת התרופה?

לטיפול בניוון שרירים שדרתי (SMA) מסוג 1, 2 ו-3 ~~במטופלים בגילאי חודשים ומעלה~~.

2. לפני שימוש בתרופה

[...]

~~**ילדים ומתבגרים**~~
~~תרופה זו אינה מיועדת לפעוטות מתחת לגיל חודשיים.~~

3. כיצד תשתמש בתרופה?

[...]

מינון
המינון ואופן הטיפול ייקבעו על-ידי הרופא בלבד. המינון המקובל בדרך כלל הוא:

גיל ומשקל גוף	מינון יומי מומלץ
מתחת לגיל חודשיים	0.15 מ"ג/ק"ג
מגיל חודשיים עד שנתיים	0.20 מ"ג/ק"ג
גיל שנתיים ומעלה (פחות מ-20 ק"ג)	0.25 מ"ג/ק"ג
גיל שנתיים ומעלה (20 ק"ג ומעלה)	5 מ"ג

6. מידע נוסף

[...]

כיצד נראית התרופה ומה תוכן האריזה?

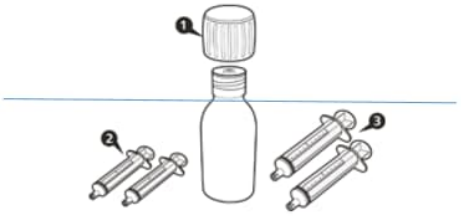
- כל אריזה מכילה בקבוק אחד, מתאם בקבוק אחד, מזרקים פומיים בצבע ענבר לשימוש רב פעמי עם סימון אשר יסייע לך למשוך את המינון הנכון –2 יחידות בנפח 1 מ"ל, 2 יחידות בנפח 6 מ"ל ו-~~2 יחידות~~ יחידה אחת בנפח 12 מ"ל.

עדכונים מהותיים בהוראות שימוש לתרופה

[...]

כל אריזה של אווריסדי מכילה (ראה/י איור א):

1. 1 בקבוק אווריסדי עם מתאם בקבוק ומכסה
2. 1 מזרק פומי בנפח 12 מ"ל
3. 2 מזרקים פומיים רב פעמיים בנפח 6 מ"ל
4. 2 מזרקים פומיים רב פעמיים בנפח ~~12~~ 1 מ"ל
5. ספרון הוראות שימוש (לא מוצג)
6. עלון לצרכן (לא מוצג)

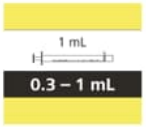


איור א

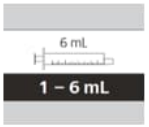
[...]

א) הכנת המנה שנרשמה לך ומשיכתה למזרק

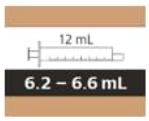
כיצד יש לבחור את המזרק הפומי המתאים למינון שנרשם עבורך



- אם המינון היומי של אווריסדי שנרשם לך או לילדך הינו בין 0.3 מ"ל ל-1 מ"ל, יש להשתמש במזרק פומי בנפח של 1 מ"ל (תווית צהובה).



- אם המינון היומי של אווריסדי שנרשם לך או לילדך הינו בין 1 מ"ל ל-6 מ"ל, יש להשתמש במזרק פומי בנפח של 6 מ"ל (תווית אפורה). ~~היוועץ ברופא או ברוקח לגבי עיגול המנה היומית שלך או של ילדך ל 0.1 מ"ל הקרוב ביותר.~~



- אם המינון היומי של אווריסדי שנרשם לך או לילדך הינו גבוה מ-6 מ"ל, יש להשתמש במזרק פומי בנפח של 12 מ"ל (תווית חומה).

היוועץ ברופא או ברוקח לגבי עיגול המנה היומית שלך או של ילדך לסימון ~~0.2 מ"ל~~ הקרוב ביותר על גבי המזרק.

איור ג