



FOR TREATMENT OF SPINAL MUSCULAR ATROPHY IN CHILDREN AND ADULTS

INTERACTIVE FACT SHEET

Genentech
A Member of the Roche Group

MEDIA INQUIRIES:
(650) 467-6800

WHAT IS EVRYSDI?

Evrysdi is a prescription medicine used to treat spinal muscular atrophy (SMA) in children and adults.

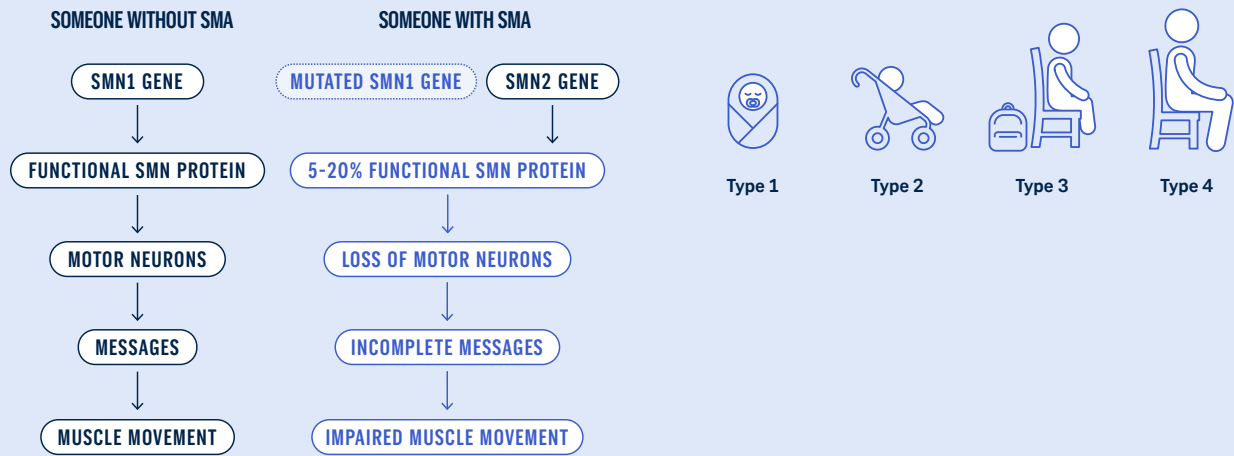
IMPORTANT SAFETY INFORMATION

- **Before taking Evrysdi, tell your healthcare provider about all of your medical conditions, including if you:**
 - are pregnant or plan to become pregnant, as Evrysdi may harm your unborn baby. Ask your healthcare provider for advice before taking this medicine

SMA is a severe, progressive neuromuscular disease that can be fatal. Approximately one in 10,000 newborns have SMA and it is among the leading genetic causes of infant mortality.

SMA is caused by a mutation in the survival motor neuron 1 (SMN1) gene that results in a **deficiency of SMN protein**, leading to the progressive loss of nerve cells (motor neurons) in the spinal cord that control muscle movement.

SMA affects people differently. There are **four primary types of SMA** (1, 2, 3 and 4) based on the age symptoms begin and the highest physical milestones reached. Disease severity is also correlated to the number of SMN2 gene copies a person has.



Depending on severity, SMA causes muscle weakness over time and can impact a person's ability to perform daily tasks such as

WALKING, EATING, BREATHING AND MANY OTHERS.



IMPORTANT SAFETY INFORMATION

• Before taking Evrysdi, tell your healthcare provider about all of your medical conditions, including if you:

- are a woman who can become pregnant:
 - Before you start your treatment with Evrysdi, your healthcare provider may test you for pregnancy
 - Talk to your healthcare provider about birth control methods that may be right for you. Use birth control while on treatment and for at least 1 month after stopping Evrysdi

Evrysdi is designed to treat SMA by

INCREASING PRODUCTION OF SMN PROTEIN

A survival of motor neuron 2 (SMN2) splicing modifier, Evrysdi is designed to treat patients with spinal muscular atrophy (SMA) caused by mutations in the survival motor neuron 1 gene on chromosome 5q that lead to SMN protein deficiency. More specifically, Evrysdi **was shown to increase the inclusion of exon 7**, a key building block for making full-length SMN protein, in SMN2 messenger RNA (mRNA).*

**Evrysdi may cause alternative splicing of additional genes*

An increase in production of full-length SMN protein is essential to the health and functioning of motor neurons and their ability to send signals to the muscles in the body to move. In clinical trials, on average, treatment with Evrysdi led to an increase in SMN protein in the blood with a greater than two-fold median change from baseline within four weeks of treatment initiation. The increase was sustained across SMA Types 1, 2 and 3 for at least 12 months of treatment. Data pertaining to increases in SMN protein in the blood for pre-symptomatic patients under two months of age are not available.

Delivery and Administration:



Delivered directly to patients via a specialty pharmacy



Strawberry-flavored liquid that can be taken by mouth once daily after a meal or breastfeeding, or given by feeding tube



Either self-administered or administered with the help of a caregiver



Recommended dose based on age and weight

IMPORTANT SAFETY INFORMATION

• **Before taking Evrysdi, tell your healthcare provider about all of your medical conditions, including if you:**

- are an adult male. Evrysdi may affect a man's ability to have children (fertility). Ask a healthcare provider for advice before taking this medicine

MORE THAN 490 PEOPLE AGED NEWBORN TO 60 YEARS

with pre-symptomatic, Type 1, 2, or 3 SMA were included in the Evrysdi clinical trial program*



*The approval of Evrysdi by the U.S. Food and Drug Administration (FDA) was based on data from three clinical studies designed to represent a broad spectrum of people living with SMA: RAINBOWFISH is an ongoing, open-label study in 26 newborns younger than 6 weeks (at first dose). These newborns were genetically diagnosed with SMA and had not yet shown symptoms (pre-symptomatic SMA); FIREFISH is a 2-part, open-label study in 62 infants aged 2 to 7 months with Type 1 SMA; SUNFISH is a 2-part, placebo-controlled study in 231 adults and children aged 2 to 25 years with Type 2 or 3 SMA.



Pre-symptomatic infants (under 6 weeks)



Symptomatic infants (2-7 months)



Children and adults of all ages



People with Type 2 or 3 SMA with scoliosis or joint contractures

For more information on the clinical studies:

In addition to FIREFISH, SUNFISH and RAINBOWFISH, one other trial for Evrysdi is ongoing:

- **JEWELFISH**, which is evaluating people with SMA aged 6 months to 60 years who received other investigational or approved SMA therapies for at least 90 days prior to receiving Evrysdi.

IMPORTANT SAFETY INFORMATION

- Before taking Evrysdi, tell your healthcare provider about all of your medical conditions, including if you:
 - are breastfeeding or plan to breastfeed. It is not known if Evrysdi passes into breast milk and may harm your baby



FIREFISH

Two-part open-label pivotal study designed to assess Evrysdi safety, tolerability and efficacy as well as the drug's movement in the body (pharmacokinetics or PK) and the body's reaction to the drug (pharmacodynamics or PD)

- Part 1 was a dose-finding study in 21 infants to assess the safety profile of Evrysdi in infants and determine the dose for Part 2. Part 2 was a pivotal, single-arm study of Evrysdi in 41 infants with Type 1 SMA treated for two years. The study enrolled symptomatic **infants aged 2 to 7 months with Type 1 SMA**
- Efficacy was established as survival without permanent ventilation and the ability to sit, specifically the proportion of **infants sitting without support for at least 5 seconds** at 12 months of treatment, assessed by the Gross Motor Scale of the Bayley Scales of Infant and Toddler Development Third Edition (BSID-III)*

Results from FIREFISH Part 2 showed:

- 29% (12/41) of infants treated with Evrysdi were able to sit without support for at least 5 seconds after 12 months of treatment, the primary endpoint of the study, as measured by Item 22 on the BSID-III gross motor scale*

Pooled data from FIREFISH showed:



After 12 months of treatment, 33% receiving the recommended dose achieved the ability to sit without support for at least 5 seconds (n=58)**



After 24 months of treatment, 60% achieved the ability to sit without support for at least 5 seconds (n=58)**



After 12 months of treatment, 87% were alive without permanent ventilation***,**** (n=62)*****



After 24 months of treatment, 84% were alive without permanent ventilation (n=62)*****

– In the natural history of infantile-onset SMA, only 25% of infants would be expected to survive without permanent ventilation beyond 14 months of age

– In the natural history of infantile-onset SMA, infants would not be expected to be able to sit independently

*BSID-III is an assessment used to evaluate development in infants and toddlers 1 to 42 months of age. The gross motor subscale was adapted for use in symptomatic infants with Type 1 SMA. Sitting was one of the motor functions measured.

**Results were pooled from all patients who received the recommended dose of Evrysdi (all patients in Part 2 and those in the high-dose cohort of Part 1; n=58).

*** Permanent ventilation defined as requiring a tracheostomy or more than 21 consecutive days of either non-invasive ventilation (\geq 16 hours per day) or intubation, in the absence of an acute reversible event

****Out of 62 patients, 6 infants died (4 within the first 3 months following study enrollment) and one additional patient withdrew from treatment and died 3.5 months later. Four patients required permanent ventilation by month 24.

*****Results were pooled from all patients who received any dose of Evrysdi in Part 1 and Part 2 (n=62)

IMPORTANT SAFETY INFORMATION

- **Tell your healthcare provider about all the medicines you take**
- You should receive Evrysdi from the pharmacy as a liquid. If the medicine in the bottle is a powder, **do not use it**. Contact your pharmacist for a replacement
- Avoid getting Evrysdi on your skin or in your eyes. If Evrysdi gets on your skin, wash the area with soap and water. If Evrysdi gets in your eyes, rinse your eyes with water



SUNFISH

Two-part, pivotal multi-center clinical trial designed to assess Evrysdi tolerability, safety, efficacy, PK and PD

- Part 1 was dose-finding and exploratory, pivotal Part 2 was randomized, double-blind and placebo-controlled
- Part 2: Primary endpoint was mean **change from baseline in the Motor Function Measure (MFM-32)[†] total score** after one year of treatment with Evrysdi, compared to placebo
- Included **people aged 2 to 25 with Type 2 or 3 SMA**
 - In Part 2, at baseline, 67% of patients had scoliosis (32% of them with severe scoliosis)
 - Patients were randomized 2:1 to receive either Evrysdi at the recommended dose or placebo

Data at month 12 from SUNFISH Part 2 showed:



Evrysdi-treated patients (n=115) had a **significantly greater change in motor function from baseline vs placebo (n=59)****, as measured by MFM-32 (1.55-point difference between the means; 95% CI: 0.30, 2.81; p=0.0156)***



Evrysdi demonstrated a 1.36-point mean change from baseline (95% CI: 0.61, 2.11) vs a -0.19-point mean change from baseline for placebo (95% CI: -1.22, 0.84)



The percentage of Evrysdi-treated patients who had a change in baseline MFM-32 total score of 3 or more (95% CI) was 38% (28.9, 47.6), compared to 24% (12.0, 35.4) for placebo



Additionally, Evrysdi treatment was shown to **improve upper limb motor function in children and adults** compared to baseline, as measured by the Revised Upper Limb Module (RULM)****, a secondary endpoint of the study (1.59 point difference; p=0.0028) between the means in Evrysdi (n=119) and placebo (n=58) groups (1.61 points [95% CI: 1.00, 2.22]; 0.02 [95% CI: -0.83, 0.87] respectively.)

* The MFM-32 scale has the ability to assess a wide range of motor function across a broad range of SMA patients; total MFM-32 score is expressed as a percentage of the maximum possible score, with higher scores indicating greater motor function. MFM-32 measures motor function abilities which relate to important daily functions

** Based on the missing data rule for MFM-32, 6 patients were excluded from the analysis (Evrysdi n=115; placebo control n=59)

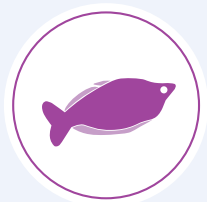
*** Evrysdi™ (risdiplam) Prescribing Information. Genentech, Inc. July 2020

**** RULM assesses the ability to push, pull, place, tear, open, raise, and lift objects, as well as hand, arm, and reaching movements in children and adults with SMA. It can capture progressive muscle weakness across the spectrum of SMA, reflective of the SUNFISH Part 2 study population

IMPORTANT SAFETY INFORMATION

• The most common side effects of Evrysdi include:

- For later-onset SMA:
 - fever
 - diarrhea
 - rash



RAINBOWFISH

Open-label, single-arm, multi-center study designed to assess Evrysdi efficacy, safety, PK and PD in babies from birth to 6 weeks of age (at first dose) with genetically diagnosed SMA who are not yet presenting with symptoms

At the time initial results were collected, 18 infants had enrolled in the study. These infants were younger than 6 weeks (between 16 and 40 days) at the time of first Evrysdi dose. Six infants had received Evrysdi for at least 12 months and were included in the measurement of effectiveness. These infants had either 2 or 3 copies of the SMN2 gene

After 12 months of treatment, data from the initial results of RAINBOWFISH showed:



100% were able to sit after one year of treatment* (n=6)



67% of the babies could stand* (n=6)



50% could walk independently* (n=6)



All infants were alive at 12 months without permanent ventilation** (n=6)

**As measured by the Hammersmith Infant Neurological Examination-Module 2 (HINE-2), which assesses 8 developmental milestones for infants, including head control, sitting, voluntary grasp, ability to kick, rolling, crawling, standing, and walking.*

***Permanent ventilation was defined as having a tracheostomy (a surgery where a tube is inserted in the front of the throat into the windpipe) or more than 21 days of either noninvasive ventilation support (16 or more hours a day) or being intubated (a procedure where a breathing tube is inserted down the throat and into the windpipe) to help with breathing, in the absence of an acute reversible event.*

IMPORTANT SAFETY INFORMATION

• The most common side effects of Evrysdi include:

o For infantile-onset SMA:

- fever
- diarrhea
- rash
- runny nose, sneezing and sore throat (upper respiratory infection)
- lung infection (lower respiratory infection)
- constipation
- vomiting
- cough

The adverse reaction profile of Evrysdi was **evaluated in pediatric and adult SMA patients** across the FIREFISH, SUNFISH and RAINBOWFISH clinical trials:

Most common adverse reactions in later-onset SMA (incidence at least 10% of Evrysdi patients and more frequently than placebo) were fever*, diarrhea and rash**



Most common adverse reactions in infantile-onset SMA were similar to those observed in later-onset SMA patients. Additionally, adverse reactions with an incidence of at least 10% were upper respiratory tract infection***, lower respiratory tract infection****, constipation, vomiting and cough

The safety profile of Evrysdi in pre-symptomatic patients was consistent with its safety profile for symptomatic SMA patients

These are not all the possible side effects of Evrysdi. For more information, patients should speak with their healthcare professional.

* Includes pyrexia and hyperpyrexia

** Includes rash, erythema, rash maculo-papular, rash erythematous, rash papular, dermatitis allergic, and folliculitis

*** Includes nasopharyngitis, rhinitis

**** Includes pneumonia, bronchitis

The Evrysdi clinical development program was led by Genentech as part of a collaboration with the SMA Foundation and PTC Therapeutics

IMPORTANT SAFETY INFORMATION

These are not all of the possible side effects of Evrysdi. For more information on the risk and benefits profile of Evrysdi, ask your healthcare provider or pharmacist. You may report side effects to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Genentech at 1-888-835-2555.

Evrysdi® (risdiplam) is approved by the FDA for the treatment of SMA in children and adults

The approval was based on a **COMPREHENSIVE CLINICAL TRIAL PROGRAM**

in people with **varying ages and levels of disease severity**, including pre-symptomatic and Types 1, 2, and 3 SMA, as seen across three clinical trials



FIREFISH: Evrysdi helped symptomatic infants **survive without permanent ventilation*** and **achieve a key motor milestone not typically seen** in the natural course of the disease

- Results from the confirmatory part of the trial showed that 29% (12/41) of infants treated with Evrysdi were able to sit without support for at least 5 seconds (as measured by Item 22 on the BSID-III gross motor scale**) after 12 months of treatment, the primary endpoint of the study
- 33% of those receiving the recommended dose achieved the ability to sit without support for at least 5 seconds at 12 months of treatment and 60% achieved the ability to sit without support for at least 5 seconds at 24 months of treatment (n=58)
- 87% were alive without permanent ventilation at 12 months of treatment and 84% were alive without permanent ventilation at 24 months of treatment (n=62)
- As described in the natural history of untreated infantile-onset SMA, infants would not be expected to be able to sit independently, and only 25% would be expected to survive without permanent ventilation beyond 14 months of age

*Permanent ventilation defined as requiring a tracheostomy or more than 21 consecutive days of either non-invasive ventilation (\leq 16 hours per day) or intubation, in the absence of an acute reversible event

**BSID-III is an assessment used to evaluate development in infants and toddlers 1 to 42 months of age. The gross motor subscale was adapted for use in symptomatic infants with Type 1 SMA. Sitting was one of the motor functions measured.

*** Based on the missing data rule for MFM-32, 6 patients were excluded from the analysis (Evrysdi n=115; placebo control n=59)



SUNFISH: In children and adults with later-onset SMA, those treated with Evrysdi (n=115) had a **significantly greater change in motor function** from baseline at 12 months vs placebo (n=59)***, as measured by MFM-32**** (1.55-point difference between the means)

- Evrysdi demonstrated a 1.36-point mean change from baseline vs a -0.19-point mean change from baseline for placebo at month 12
- The proportion of patients achieving a change from baseline total score of 3 or more was 38% for Evrysdi and 24% for placebo
- Patients treated with Evrysdi (n=119) also achieved a significantly greater change in motor function from baseline at 12 months compared to placebo (n=58), as measured by the Revised Upper Limb Module (RULM)*****



RAINBOWFISH: In infants with pre-symptomatic SMA, who have a genetic diagnosis of SMA but are not yet presenting symptoms, the majority of those with 2 or 3 copies of SMN2 treated with Evrysdi (n=6) **achieved key milestones such as sitting (100%) and standing (67%) with half walking after 12 months of treatment, as measured by Section 2 of the Hammersmith Infant Neurological Examination (HINE-2)*******



The most common adverse reactions in children and adults with Type 2 or 3 SMA were fever, diarrhea and rash. The most common side effects in infants with Type 1 SMA were fever, diarrhea, rash, runny nose/sneezing/sore throat (upper respiratory infection), lung infection (lower respiratory infection), constipation, vomiting and cough. The safety profile of Evrysdi was similar in pre-symptomatic babies



More than 1,800 people in the US with SMA are taking Evrysdi, representing a **broad spectrum of people living with SMA**



The 1st and only **at-home administered treatment for SMA**

****The MFM-32 scale has the ability to assess a wide range of motor function across a broad range of SMA patients; total MFM-32 score is expressed as a percentage of the maximum possible score, with higher scores indicating greater motor function. MFM-32 measures motor function abilities which relate to important daily functions

*****RULM is a scale designed to assess upper limb movement in people with SMA

*****HINE-2 is an assessment to test whether infants or young children are able to reach motor milestones

IMPORTANT SAFETY INFORMATION

Please see full [Prescribing Information](#) for additional Important Safety Information.

Distributed by: Genentech, Inc., A Member of the Roche Group, 1 DNA Way, South San Francisco, CA 94080-4990
Evrysdi® is a registered trademark of Genentech, Inc.

©2022 Genentech, Inc. All rights reserved.

For more information, go to www.Evrysdi.com or call 1-833-387-9734.