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.

Please see full Prescribing Information for additional Important Safety Information.
Many people with spinal muscular atrophy (SMA) have made the move

1,800+

people in the US with SMA are taking Evrysdi, including people up to 84 years old*†

*Number of people taking Evrysdi as of May 2022. Evrysdi approved in August 2020.
†Clinical studies of Evrysdi did not include people aged 65 and older to determine whether they respond differently from those who are younger.

Please see full Prescribing Information for additional Important Safety Information.
The progression of SMA is **relentless**

SMA is caused by a shortage of the survival motor neuron (SMN) protein, which your muscles need to function.

As a result, muscles throughout your body continuously weaken.

This may lead to:

- Difficulty swallowing
- Difficulty eating
- Loss of motor function (for example, losing the ability to walk)
- Challenges breathing

... and may cause complications with your bones, joints, and spine over time.

This happens to people with Types 1, 2, and 3 SMA, even if you don’t notice day-to-day changes.

“**It wasn’t until I started to lose my hand strength that I decided to go talk to my doctor about treatment.**”

**Christa**, living with Type 2 SMA

Please see full Prescribing Information for additional Important Safety Information.
Important Safety Information (continued)

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

Please see full Prescribing Information for additional Important Safety Information.

Treatment matters

Disease-modifying treatments may:

- Increase SMN protein
- Help slow disease progression
- Help maintain or improve motor function
- Fit into your routine

SMN stands for survival motor neuron.

You do have choices

“...to seek out treatment. Talk to your doctor. It can give you hope.”

Dan, living with Type 2 SMA
SMN protein plays a **critical role** throughout the body

The **human body needs a key protein** called survival motor neuron, or SMN, for our muscles to function properly.

SMN protein has several important jobs within the cells that ultimately enable our bodies to move.

It is found in all cells and tissues in the body, including muscle cells.

**People with SMA have low levels of this protein, causing muscles to break down.** This has a widespread impact ... from head to toe.

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**Important Safety Information (continued)**

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

- are a woman who can become pregnant:
  - **Pregnancy Registry.** Talk to your healthcare provider right away if you become pregnant while taking Evrysdi. Ask about registering with the Evrysdi Pregnancy Registry, which was created to collect information about your health and your baby's health. Your healthcare provider can enroll you in this registry by calling 1-833-760-1098 or visiting www.evrysdipregnancyregistry.com

Please see full Prescribing Information for additional Important Safety Information.
Designed to help the body **make more SMN protein**

Within 4 weeks of treatment with Evrysdi, SMN protein levels in the blood **more than doubled**, and they **were maintained** for Types 1, 2, and 3 SMA throughout 2 years of the studies.*

When studied in animals, this protein was distributed throughout the body.

*No data available in presymptomatic SMA (under 2 months).
SMN stands for survival motor neuron, MOA stands for mechanism of action.

**Important Safety Information (continued)**

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.

Please see full Prescribing Information for additional Important Safety Information.
More than 490 people aged newborn to 60 years with presymptomatic, Type 1, 2, or 3 SMA*

Efficacy is being studied in people aged 16 days to 25 years, and safety is being studied in people aged 16 days to 60 years.

*RAINBOWFISH is an 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 (presymptomatic 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. JEWELFISH is an open-label safety study in 174 people aged 1 to 60 years with Type 1, 2, or 3 SMA that was previously treated with approved or investigational SMA medications.

†In SUNFISH Part 1, 7 people were able to walk; in JEWELFISH, 16.

Important Safety Information (continued)

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

Please see full Prescribing Information for additional Important Safety Information.
POSSIBILITY AHEAD

Evrysdi keeps working so we can keep reaching

Important Safety Information (continued)
Tell your healthcare provider about all the medicines you take. Please see full Prescribing Information for additional Important Safety Information.
A closer look at the SUNFISH study

SUNFISH is a 2-part, placebo-controlled study in adults and children with Type 2 or 3 SMA

SUNFISH PART 1

51 adults and children (2 to 24 years)
- Explored the dose and safety of Evrysdi
- Included 7 people who could walk

SUNFISH PART 2

180 adults and children (2 to 25 years)
- Measured the safety and effectiveness of the recommended dose of Evrysdi (in 120 people), compared with placebo (in 60 people)
- Included 180 people who were not able to walk, 120 people with scoliosis (57 with severe scoliosis), and people with and without joint contractures

Main measurement after 12 months of taking Evrysdi:
Change in motor function* with Evrysdi, compared with placebo

231 adults and children with Type 2 or 3 SMA

The majority of people in the SUNFISH study would not have qualified for prior SMA studies

Important Safety Information (continued)

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.

Please see full Prescribing Information for additional Important Safety Information.

*Measured by the Motor Function Measure-32 Items (MFM-32) scale.
†Adults and children not taking Evrysdi took a placebo, a substance that has no active medication and is often used in studies.
MFM-32 measures **motor function** related to important daily functions.

The MFM-32 scale includes motor movement across 3 categories:

- **Standing/transfer movements**
- **Upper/lower body movements**
- **Hand/foot movements**

**What is MFM-32?**

The **Motor Function Measure–32 Items** (MFM-32) scale evaluates 32 different elements to assess head, trunk, and limb motor movement.

This scale is designed to capture change for a broad range of people, including those who can and cannot walk.

Please see full Prescribing Information for additional important Safety Information.
**Evrysdi improved or preserved motor skills**

**EVRYSIDI IN ADULTS AND CHILDREN**

**Change in motor function score over 12 months vs placebo**

As measured by MFM-32

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Average score increased 1.36 points with Evrysdi

Average score decreased 0.19 points with placebo

1.55-point estimated improvement vs placebo

(95% CI: 0.30, 2.81; \( P = 0.0156 \))

---

"Since starting Evrysdi, I have noticed changes in my motor function. I can push up on my arms and stand when transferring out of my wheelchair."

Shaniqua, living with Type 3 SMA

---

*In some studies, including this one, if someone’s data cannot be collected on time for any reason, that person’s progress cannot be counted in that part of the study. This chart includes only the information that was collected on time.

†Adults and children not taking Evrysdi took a placebo, a substance that has no active medication and is often used in studies.

‡This 95% CI (confidence interval) means that we are 95% confident that the actual average change in MFM-32 with Evrysdi will be between 0.30 and 2.81 points higher than with placebo. MFM-32 stands for the Motor Function Measure-32 Items.

**Important Safety Information (continued)**

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.

*Please see full Prescribing Information for additional Important Safety Information.*
### Exploratory observations: change in motor function score over 2 years

**Change in motor function score over 24 months**

As measured by MFM-32

- **Evrysdi** (0-24 months)
- **Placebo**† (0-12 months)

<table>
<thead>
<tr>
<th>Evrysdi (n)</th>
<th>Placebo (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>115</td>
<td>59</td>
</tr>
<tr>
<td>113</td>
<td>57</td>
</tr>
<tr>
<td>113</td>
<td>58</td>
</tr>
<tr>
<td>112</td>
<td>58</td>
</tr>
<tr>
<td>107</td>
<td>103</td>
</tr>
</tbody>
</table>

1.83-point average change in MFM-32 score from the start of the study with Evrysdi

This information is considered **exploratory**. This means it was not designed to show a treatment effect so conclusions cannot be drawn.

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**Important Safety Information (continued)**

The most common side effects of Evrysdi include:
- For later-onset SMA: fever, diarrhea, rash

Please see full Prescribing Information for additional **Important Safety Information**.
More adults and children experienced a ≥3-point change with Evrysdi compared with placebo after 1 year.

**Change in motor function score after 12 months**

As measured by MFM-32

<table>
<thead>
<tr>
<th>Improvement (≥3-point change)</th>
<th>Stabilization† or improvement (≥0-point change)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Evrysdi</strong></td>
<td><strong>Stabilization† or improvement</strong></td>
</tr>
<tr>
<td>38% (44/115)</td>
<td>70% (80/115)</td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td><strong>Placebo</strong></td>
</tr>
<tr>
<td>24% (14/59)</td>
<td>54% (32/59)</td>
</tr>
</tbody>
</table>

\[P=0.0469\]

†Results in stabilization were not one of the main measurements and were only considered supportive. This means it was not designed to show a treatment effect so conclusions cannot be drawn.

A 3-point change may represent the ability to perform an everyday task. Depending on their starting score, for some, this could mean having the ability to wash their face, put on pants, or get into bed.

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**Important Safety Information (continued)**

The most common side effects of Evrysdi include:

- For infantile-onset SMA: fever; diarrhea; rash; runny nose, sneezing, and sore throat (upper respiratory infection); lung infection (lower respiratory infection); constipation; vomiting; cough

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.

Please see full Prescribing Information for additional Important Safety Information.

*In some studies, including this one, if someone's data cannot be collected on time for any reason, that person's progress cannot be counted in that part of the study.

This chart includes only the information that was collected on time.

MFM-32 stands for the Motor Function Measure-32 Items.
RULM evaluates **upper limb strength** and the ability to perform daily tasks

The RULM assessment includes tests such as:

- Picking up tokens
- Placing a coin or other small object into a cup
- Pushing a button
- Using a pencil
- Tearing paper
- Reaching to the side
- Raising a cup to mouth
- Bringing hands from lap to table
- Bringing a hand to shoulder
- Bringing a hand above shoulder
- Bringing both arms above head
- Opening a container
- Lifting and moving 1/2-lb and 1-lb weights*
- Bringing a 1-lb weight from lap to table or eye level*
- Bringing 1-lb and 2-lb weights above shoulder*
- Opening a container
- Lifting and moving 1/2-lb and 1-lb weights*
- Bringing a 1-lb weight from lap to table or eye level*
- Bringing 1-lb and 2-lb weights above shoulder*

*Weight is approximate and has been converted from grams to pounds.

Please see full Prescribing Information for additional Important Safety Information.

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**What is RULM?**

The **Revised Upper Limb Module (RULM)** evaluates strength in arm movements and the ability to perform specific tasks. It was specifically designed for people 2.5 years and older living with SMA who have varying levels of muscle weakness.
Evrysdi improved upper limb strength important for activities of everyday life

“With Evrysdi, I’ve noticed real improvements — plus, it’s an oral treatment I can take at home!”

Christa, living with Type 2 SMA

**EVRYSDI IN ADULTS AND CHILDREN**

Change in upper limb score over 12 months vs placebo
As measured by RULM

![Graph showing change in RULM total score from the start of the study](image)

- **1.61-point increase** with Evrysdi
- **0.02-point increase** with placebo

1.59-point estimated improvement vs placebo
(95% CI: 0.55, 2.62; P=0.0469)‡

### Important Safety Information (continued)

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

Please see full Prescribing Information for additional Important Safety Information.

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*In some studies, including this one, if someone’s data cannot be collected on time for any reason, that person’s progress cannot be counted in that part of the study. This chart includes only the information that was collected on time.
†Adults and children not taking Evrysdi took a placebo, a substance that has no active medication and is often used in studies.
‡This 95% CI (confidence interval) means that we are 95% confident that the actual average change in RULM with Evrysdi will be between 0.55 and 2.62 points higher than with placebo.
RULM stands for the Revised Upper Limb Module (RULM) assessment.
Important Safety Information (continued)
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

This information is considered exploratory. This means it was not designed to show a treatment effect so conclusions cannot be drawn.

2.79-point average change in RULM score from the start of the study with Evrysdi

Exploratory observations: change in upper limb function over 2 years

Change in upper limb score over 24 months
As measured by RULM

Average change in RULM total score from the start of the study

<table>
<thead>
<tr>
<th>Visit (months)</th>
<th>Evrysdi (n)</th>
<th>Placebo (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>117</td>
<td>108</td>
</tr>
<tr>
<td>18</td>
<td>116</td>
<td>105</td>
</tr>
<tr>
<td>24</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Evrysdi* (0-24 months)
Placebo*† (0-12 months)

*In some studies, including this one, if someone's data cannot be collected on time for any reason, that person's progress cannot be counted in that part of the study. This chart includes only the information that was collected on time.
†Adults and children not taking Evrysdi took a placebo, a substance that has no active medication and is often used in studies. People in this group received placebo for 12 months followed by Evrysdi for 12 months. The period of time on Evrysdi is not included in this chart. The follow-up period was not placebo controlled.
RULM stands for the Revised Upper Limb Module (RULM) assessment.

Please see full Prescribing Information for additional Important Safety Information.
Important Safety Information (continued)

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

- are a woman who can become pregnant:
  - Pregnancy Registry. Talk to your healthcare provider right away if you become pregnant while taking Evrysdi. Ask about registering with the Evrysdi Pregnancy Registry, which was created to collect information about your health and your baby’s health. Your healthcare provider can enroll you in this registry by calling 1-833-760-1098 or visiting www.evrysdipregnancyregistry.com

Please see full Prescribing Information for additional Important Safety Information.
A closer look at the FIREFISH study

62 infants with Type 1 SMA

Main measurements after 12 months of taking Evrysdi:
- Sitting without support for at least 5 seconds*
- Survival without permanent breathing support†

FIREFISH is a 2-part, open-label study in infants with Type 1 SMA

FIREFISH is made up of 2 parts:

PART 1
Explored the recommended dose of Evrysdi in 21 infants (aged 3 to 7 months)

PART 2
Measured the safety and effectiveness of Evrysdi in 41 infants (aged 2 to 7 months) at the recommended dose

58 infants (aged 2 to 7 months) who received the recommended dose of Evrysdi in Parts 1 and 2 were included in a pooled analysis that evaluated the effectiveness of Evrysdi

†Permanent support 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.

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

Please see full Prescribing Information for additional Important Safety Information.
Changing the course of SMA by helping infants **sit without support** for at least 5 seconds

Of the infants taking the recommended dose of Evrysdi

| FIREFISH PART 2  
(MAIN MEASUREMENT) | FIREFISH PARTS 1 AND 2 | AFTER 2 YEARS |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>AFTER 1 YEAR</td>
<td>AFTER 1 YEAR</td>
<td>AFTER 2 YEARS</td>
</tr>
<tr>
<td><strong>29%</strong></td>
<td><strong>33%</strong></td>
<td><strong>60%</strong></td>
</tr>
</tbody>
</table>

of infants (12/41)  
of infants (19/58)  
of infants (35/58)

were able to sit without support **for at least 5 seconds**

These results were measured using the **Bayley Scales of Infant and Toddler Development-Third Edition (BSID-III)** gross motor scale, which assesses a range of physical abilities such as sitting, rolling, and crawling.

Important Safety Information (continued)

**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

Please see full Prescribing Information for additional Important Safety Information.
Remarkable achievement of **key milestones** not typically seen in infants without treatment

Of the infants taking the recommended dose of Evrysdi

- **AFTER 2 YEARS** 40% of infants (23/58) were able to sit without support for at least 30 seconds
  - As measured by BSID-III

- **AFTER 2 YEARS** 28% of infants (16/58) were able to stand
  - As measured by HINE-2
  - 9/58 could stand supporting weight
  - 7/58 could stand with support

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


**Important Safety Information (continued)**

Tell your healthcare provider about all the medicines you take.

Please see full Prescribing Information for additional **Important Safety Information**.
Evrysdi slowed disease progression of SMA

Of the infants taking Evrysdi (all dose strengths)

AFTER 1 YEAR
87%
of infants (54/62)
were alive and able to breathe without permanent support*

AFTER 2 YEARS
84%
of infants (52/62)
were alive and able to breathe without permanent support*

Without treatment, infants with Type 1 SMA are not expected to survive beyond 14 months of age without permanent breathing support.

*Permanent support 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 (continued)
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.

Please see full Prescribing Information for additional Important Safety Information.
Additional exploratory observations: eating and swallowing

Of the infants taking the recommended dose of Evrysdi

**AFTER 1 YEAR**

85% of infants (49/58) were able to eat by mouth*

86% of infants (50/58) were able to swallow†

**AFTER 2 YEARS**

83% of infants (48/58) were able to eat by mouth*

86% of infants (50/58) were able to swallow†

This information is considered exploratory. This means it was not designed to show a treatment effect so conclusions cannot be drawn.

*Includes infants who could eat by mouth or in combination with a feeding tube.
†One infant was not able to swallow at the start of the study.

Important Safety Information (continued)

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.

Please see full Prescribing Information for additional Important Safety Information.
Important Safety Information (continued)
The most common side effects of Evrysdi include:
• For later-onset SMA: fever, diarrhea, rash

Please see full Prescribing Information for additional Important Safety Information.
The most common side effects of Evrysdi include:

- For infantile-onset SMA: fever; diarrhea; rash; runny nose, sneezing, and sore throat (upper respiratory infection); lung infection (lower respiratory infection); constipation; vomiting; cough

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.

Please see full Prescribing Information for additional Important Safety Information.
Evrysdi helped infants sit, stand, or walk

AFTER 1 YEAR

100% of infants (6/6) were able to sit

• 5/6 infants could pivot/rotate
• 1/6 infants achieved stable sit

AFTER 1 YEAR

67% of infants (4/6) were able to stand

• 3/6 infants could stand unaided
• 1/6 infants could stand with support

AFTER 1 YEAR

50% of infants (3/6) were able to walk independently

These results were measured using 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.

Important Safety Information (continued)
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

Please see full Prescribing Information for additional Important Safety Information.
Important Safety Information (continued)
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

Please see full Prescribing Information for additional Important Safety Information.
Established safety profile in adults, children, and infants with SMA

The most common side effects include:

**IN INFANTS**
Type 1 SMA (infantile-onset)

- fever
- diarrhea
- rash

**IN ADULTS AND CHILDREN**
Type 2 or 3 SMA (later-onset)

- fever
- diarrhea
- rash

- lung infection (lower respiratory infection)
- constipation
- vomiting
- cough

- Runny nose, sneezing, and sore throat
- (upper respiratory infection)

- Lung infection (lower respiratory infection)
- Constipation
- Vomiting
- Cough

- Runny nose, sneezing, and sore throat
- (upper respiratory infection)

- No one in the clinical studies stopped taking Evrysdi because of side effects of treatment*

- These are not all of the possible side effects of Evrysdi

- Safety of Evrysdi in people with SMA that was previously treated with approved or investigational SMA medications is currently being studied

- 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

For more information on the risk and benefits profile of Evrysdi, ask your healthcare provider or pharmacist.

*As of March 2022.

Please see full Prescribing Information for additional Important Safety Information.
An oral treatment that can be taken at home

Delivered directly to you  
 Stored in the refrigerator  
 Taken once a day by mouth or feeding tube

✓ Your healthcare provider will determine the right dose for you, using your age and weight. Always take the dose exactly as prescribed.

✓ You can administer Evrysdi yourself or with the help of the person who cares for you. Take your Evrysdi around the same time each day after a meal.

✓ Please read the full Patient Information and Instructions for Use that come with your prescription and discuss with your healthcare provider before taking the first dose.

Important Safety Information (continued)

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

• are a woman who can become pregnant:
  - Pregnancy Registry. Talk to your healthcare provider right away if you become pregnant while taking Evrysdi. Ask about registering with the Evrysdi Pregnancy Registry, which was created to collect information about your health and your baby’s health. Your healthcare provider can enroll you in this registry by calling 1-833-760-1098 or visiting www.evrysdipregnancyregistry.com

Please see full Prescribing Information for additional Important Safety Information.
Support along the way

MySMA Support* is a support service from Genentech that can help answer your questions, navigate insurance coverage, and explain financial assistance options, to help you start and stay on Evrysdi.

Partnership and Access Liaisons (PALs) are here to help:
A PAL is your local Genentech representative who supports people living with SMA and their caregivers. A PAL can:

- Provide in-person or virtual support based on your preference
- Explain insurance coverage and potential financial support options
- Answer questions about Evrysdi, including how it works, how to take it, what results were seen in clinical trials, and important safety information
- Refer you to helpful resources

Talk to a PAL in person, over the phone, or online.

Connect with a local PAL by visiting Evrysdi.com/PAL or calling (833) 387-9734 (Monday-Friday, 9 am to 8 pm ET).

We’re here to help!

MySMA Support, including the PAL, does not provide medical advice and is not a substitute for your medical team. Your healthcare provider should always be your main resource for any questions about your health and medical care.

*Enrollment in MySMA Support through the Evrysdi Start Form is mandatory to receive assistance through the program. Participation in MySMA Support is not necessary to receive treatment with Evrysdi.

Please see full Prescribing Information for additional Important Safety Information.
Powerful results for everyday life

✓ Proven results in individuals with Type 1, 2, 3 or presymptomatic SMA

SEE DETAILS ON NEXT PAGES

✓ Designed to help the body make more SMN protein

✓ Safety profile that has been studied in more than 490 people from newborns to adults

✓ Oral treatment that can fit into your day

Talk with your healthcare provider to learn more

SMN stands for survival motor neuron.

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

Important Safety Information (continued)
Before taking Evrysdi, tell your doctor if you are pregnant or plan to become pregnant, or are breastfeeding or plan to breastfeed. Evrysdi may harm an unborn or breastfed baby. Evrysdi may affect a man's ability to have children (fertility). Tell your doctor about all the medicines you take.

Please see full Prescribing Information for additional Important Safety Information.
Adults and children with Type 2 or 3 SMA improved their abilities and strength

**AFTER 1 YEAR**

- **Motor function improved** (average 1.36-point increase on the MFM-32 scale with Evrysdi vs average 0.19-point decrease with placebo)
  - 1.55-point estimated improvement vs placebo on the MFM-32 scale (95% CI: 0.30, 2.81; \(P=0.0156\))

- **Strength in arm and hand movement improved** (average 1.61-point increase on the RULM scale with Evrysdi vs average 0.02-point increase with placebo)
  - 1.59-point difference (95% CI: 0.55, 2.62) between the means (\(P=0.0469\))

Most common side effects of Evrysdi in adults and children with Type 2 or 3 SMA include: fever, diarrhea, and rash

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SMN stands for survival motor neuron.

**What is Evrysdi?**
Evrysdi is a prescription medicine used to treat spinal muscular atrophy (SMA).

**Important Safety Information (continued)**
Before taking Evrysdi, tell your doctor if you are pregnant or plan to become pregnant, or are breastfeeding or plan to breastfeed. Evrysdi may harm an unborn or breastfed baby. Evrysdi may affect a man’s ability to have children (fertility). Tell your doctor about all the medicines you take.

Please see full Prescribing Information for additional important Safety Information.
In infants with Type 1 SMA,

**Evrysdi empowered survival and development**

- **In FIREFISH PART 2 (MAIN MEASUREMENT)**
  - 29% of infants (12/41) after 1 year were **able to sit without support for at least 5 seconds**, as measured by BSID-III

- **In FIREFISH PARTS 1 AND 2 (POOLED ANALYSIS)**
  - 33% of infants (19/58) after 1 year and 60% of infants (35/58) after 2 years were **able to sit without support for at least 5 seconds**, as measured by BSID-III
  - 28% of infants (16/58) after 2 years were **able to stand**, as measured by HINE-2
  - 87% of infants (54/62) after 1 year and 84% of infants (52/62) after 2 years were **alive and able to breathe without permanent support**

Most common side effects of Evrysdi in infants with Type 1 SMA include: fever; diarrhea; rash; runny nose, sneezing, and sore throat (upper respiratory infection); lung infection (lower respiratory infection); constipation; vomiting; cough

*Permanent support 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.

Powerful results for everyday life

Proven results in individuals with Type 1, 2, 3 or presymptomatic SMA

Designed to help the body make more SMN protein

Safety profile that has been studied in more than 490 people from newborns to adults

Oral treatment that can fit into your day

SEE DETAILS ON NEXT PAGES

Talk with your healthcare provider to learn more

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SMN stands for survival motor neuron.

What is Evrysdi?
Evrysdi is a prescription medicine used to treat spinal muscular atrophy (SMA).

Important Safety Information (continued)
Before taking Evrysdi, tell your doctor if you are pregnant or plan to become pregnant, or are breastfeeding or plan to breastfeed. Evrysdi may harm an unborn or breastfed baby. Evrysdi may affect a man’s ability to have children (fertility). Tell your doctor about all the medicines you take.

Please see full Prescribing Information for additional Important Safety Information.

Newborns diagnosed with presymptomatic SMA achieved important milestones

AFTER 1 YEAR

- 100% of infants (6/6) were able to sit (5 could pivot/rotate and 1 achieved stable sit)
- 67% of infants (4/6) were able to stand (3 unaided; 1 with support)
- 50% of infants (3/6) were able to walk independently

As measured by HINE-2 in presymptomatic infants.

The safety profile of Evrysdi in infants treated before symptoms of SMA appear was consistent with the safety profile of Evrysdi in infants with Type 1 SMA and adults and children with Type 2 or 3 SMA

HINE-2 stands for Hammersmith Infant Neurological Examination–Module 2.
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
- 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
- Pregnancy Registry. Talk to your healthcare provider right away if you become pregnant while taking Evrysdi. Ask about registering with the Evrysdi Pregnancy Registry, which was created to collect information about your health and your baby’s health. Your healthcare provider can enroll you in this registry by calling 1-833-760-1098 or visiting www.evrysdipregnancyregistry.com
- 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
- are breastfeeding or plan to breastfeed. It is not known if Evrysdi passes into breast milk and may harm your baby

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.

The most common side effects of Evrysdi include:

- For later-onset SMA: fever, diarrhea, rash
- For infantile-onset SMA: fever; diarrhea; rash; runny nose, sneezing, and sore throat (upper respiratory infection); lung infection (lower respiratory infection); constipation; vomiting; cough

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.

Please see full Prescribing Information for additional Important Safety Information.
ADDITIONAL INFORMATION

Please see full Prescribing Information for additional Important Safety Information.
Evrysdi increased and maintained SMN protein levels, regardless of SMA type*

Within 4 weeks, SMN protein levels more than doubled across all SMA types, throughout 12 months of studies

*Types 1, 2, and 3. No data available in presymptomatic SMA (under 2 months). SMN stands for survival motor neuron.

Important Safety Information (continued)

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

Please see full Prescribing Information for additional Important Safety Information.
People with SMA are **missing an important protein**

SMA is a genetic condition that causes muscles throughout the body to break down. This happens when the body can’t produce a key protein called “survival motor neuron,” or SMN, which is needed for nerves to function properly.

Think of SMA like a cellphone network with a service outage: an important tower is down, and some communications may not be able to get through.

In a person with SMA, this tower is the **SMN1** gene, which is one of the genes responsible for producing SMN protein.

The **SMN2** gene is the backup tower for this network: when the main tower is down, it can help you connect, but not as well.

SMN stands for survival motor neuron.

**Important Safety Information (continued)**

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

Please see full Prescribing Information for additional Important Safety Information.
How Evrysdi works

Evrysdi is designed to make and maintain more SMN protein.

Evrysdi supports the SMN2 backup tower, helping improve the signal so more calls can go through when the SMN1 gene isn’t functioning.

Evrysdi helps the SMN2 gene produce more SMN protein.

Within 4 weeks of taking Evrysdi, SMN protein levels in the blood more than doubled for Types 1, 2, and 3 SMA.* These increases were maintained throughout 2 years of the studies.

*No data available in presymptomatic SMA.
SMN stands for survival motor neuron.

Important Safety Information (continued)
Tell your healthcare provider about all the medicines you take.
Please see full Prescribing Information for additional Important Safety Information.
JEWELFISH description of study participants

**All participants** (N=174)

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at enrollment, years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>14.0 (1-60)</td>
<td></td>
</tr>
<tr>
<td>≥18 years, % (n)</td>
<td>36% (63)</td>
<td></td>
</tr>
<tr>
<td>Gender, % (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>55% (95)</td>
<td></td>
</tr>
<tr>
<td>SMA type, % (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>9% (15)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>62% (108)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>29% (51)</td>
<td></td>
</tr>
<tr>
<td>SMN2 copy number, % (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1% (1)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>7% (12)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>78% (136)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>13% (22)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>2% (3)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease severity</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Scoliosis, % (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>83% (139)†</td>
<td></td>
</tr>
<tr>
<td>&gt;40° curvature</td>
<td>39% (66)†</td>
<td></td>
</tr>
<tr>
<td>Hip - partial or complete dislocation, % (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>30% (51)‡</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Motor function assessment scores at baseline</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor function at baseline, % (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsitters</td>
<td>34% (59)†</td>
<td></td>
</tr>
<tr>
<td>Sitters</td>
<td>57% (99)†</td>
<td></td>
</tr>
<tr>
<td>Walkers</td>
<td>9% (16)</td>
<td></td>
</tr>
<tr>
<td>Baseline HFMSE total score &lt;10, % (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>63% (105)‡</td>
<td></td>
</tr>
</tbody>
</table>

*Only reported for people aged 2 to 60 years.
†n=168.
‡For people younger than 2 years, baseline motor milestones were evaluated by the Hammersmith Infant Neurological Examination–Module 2.
§All but 3 patients enrolled in JEWELFISH received previous treatment; these 3 patients were previously enrolled in a different trial but received placebo only.
HFMSE stands for Hammersmith Functional Motor Score Expanded.

JEWELFISH is an open-label safety study in 174 people aged 1 to 60 years with Type 1, 2, or 3 SMA that was previously treated with other approved or investigational SMA medications.§

**Important Safety Information (continued)**

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.

**Please see full Prescribing Information for additional Important Safety Information.**
All participants (N=173)*

<table>
<thead>
<tr>
<th>Side effects occurring in ≥8% of individuals, † (%) (n)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infection</td>
<td>17%</td>
<td>(30)</td>
</tr>
<tr>
<td>Fever (pyrexia)</td>
<td>17%</td>
<td>(30)</td>
</tr>
<tr>
<td>Headache</td>
<td>16%</td>
<td>(28)</td>
</tr>
<tr>
<td>Nausea</td>
<td>12%</td>
<td>(20)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>11%</td>
<td>(19)</td>
</tr>
<tr>
<td>Common cold (nasopharyngitis)</td>
<td>10%</td>
<td>(17)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>8%</td>
<td>(14)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Serious side effects occurring in &gt;2% of individuals, † (%) (n)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>2%</td>
<td>(4)</td>
</tr>
<tr>
<td>Lower respiratory tract infection</td>
<td>2%</td>
<td>(3)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>2%</td>
<td>(3)</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>2%</td>
<td>(3)</td>
</tr>
</tbody>
</table>

Based on data collected through January 29, 2021.

- The length of time on Evrysdi varies for each person. Therefore, one should not compare the overall rates of common and serious side effects.

*One person withdrew from the study at baseline; therefore, 173 patients received Evrysdi.
†Multiple occurrences of the same adverse event in one person are counted only once.

Important Safety Information (continued)
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.

Please see full Prescribing Information for additional Important Safety Information.
### Exploratory observations: change in motor function score over 3 years

**Change in motor function score over 36 months**

As measured by MFM-32

![Graph showing change in motor function score over 36 months](image)

<table>
<thead>
<tr>
<th>Visit (months)</th>
<th>Evrysdi* (0-36 months)</th>
<th>Placebo**† (0-12 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>0.5</td>
<td>-0.5</td>
</tr>
<tr>
<td>12</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>18</td>
<td>1.5</td>
<td>1</td>
</tr>
<tr>
<td>24</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>30</td>
<td>2.5</td>
<td>2</td>
</tr>
<tr>
<td>36</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

| Evrysdi (n)  | 115         | 113         | 113         | 107         | 103         | 84          | 93          |
| Placebo (n)  | 59          | 57          | 58          |             |             |             |             |

1.42-point average change in MFM-32 score from the start of the study with Evrysdi

This information is considered **exploratory**. This means it was not designed to show a treatment effect so conclusions cannot be drawn.

---

*In some studies, including this one, if someone's data cannot be collected on time for any reason, that person's progress cannot be counted in that part of the study. This chart includes only the information that was collected on time.

†Adults and children not taking Evrysdi took a placebo, a substance that has no active medication and is often used in studies. People in this group received placebo for 12 months followed by Evrysdi for 12 months. The period of time on Evrysdi is not included in this chart. The follow-up period was not placebo controlled. After 24 months, participants had the opportunity to enter the open-label extension portion of the study.

MFM-32 stands for the Motor Function Measure–32 Items.

**Important Safety Information (continued)**

The most common side effects of Evrysdi include:

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

Please see full Prescribing Information for additional Important Safety Information.
Exploratory observations: change in upper limb function over 3 years

2.25-point average change in RULM score from the start of the study with Evrysdi

This information is considered exploratory. This means it was not designed to show a treatment effect so conclusions cannot be drawn.

Important Safety Information (continued)

The most common side effects of Evrysdi include:
- For infantile-onset SMA: fever; diarrhea; rash; runny nose, sneezing, and sore throat (upper respiratory infection); lung infection (lower respiratory infection); constipation; vomiting; cough

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.

Please see full Prescribing Information for additional Important Safety Information.
Safety information in infants with Type 1 SMA

The most common side effects of Evrysdi for infantile-onset SMA include:

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

No treatment-related side effects leading to withdrawal or treatment discontinuation over 24 months.

SIDE EFFECTS OCCURRING IN ≥10% OF INFANTS RECEIVING EVRYSDI

Of the infants taking Evrysdi (all dose strengths; N=62)

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Evrysdi (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infection</td>
<td>82%</td>
</tr>
<tr>
<td>Fever</td>
<td>55%</td>
</tr>
<tr>
<td>Lower respiratory tract infection</td>
<td>53%</td>
</tr>
<tr>
<td>Rash</td>
<td>29%</td>
</tr>
<tr>
<td>Constipation</td>
<td>26%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>19%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>18%</td>
</tr>
<tr>
<td>Cough</td>
<td>13%</td>
</tr>
<tr>
<td>Teething</td>
<td>13%</td>
</tr>
</tbody>
</table>

Based on data collected through November 12, 2020.

Please see full Prescribing Information for additional Important Safety Information.
### SIDE EFFECTS OCCURRING IN ≥5% OF ADULTS AND CHILDREN RECEIVING EVRYSIDI AND WITH AN INCIDENCE OF ≥5% COMPARED WITH PLACEBO (N=180)

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Evrysdi (n=120)</th>
<th>Placebo (n=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>22%</td>
<td>17%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>17%</td>
<td>8%</td>
</tr>
<tr>
<td>Rash</td>
<td>17%</td>
<td>2%</td>
</tr>
<tr>
<td>Mouth and canker sores</td>
<td>7%</td>
<td>0%</td>
</tr>
<tr>
<td>Joint pain</td>
<td>5%</td>
<td>0%</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>5%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Based on data collected through September 6, 2019.

Fever, diarrhea, and rash were the most common side effects reported more frequently than placebo that occurred in at least 10% of people taking Evrysdi.

Please see full Prescribing Information for additional Important Safety Information.
SAFETY OBSERVATIONS OVER 3 YEARS

<table>
<thead>
<tr>
<th></th>
<th>Placebo 0-12 months (n=60)*</th>
<th>Evrysdi 0-12 months (n=120)</th>
<th>Evrysdi 12-24 months (n=120)</th>
<th>Evrysdi 24-36 months (n=120)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Most common side effects, % (n)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>30.0% (18)</td>
<td>31.7% (38)</td>
<td>15.8% (19)</td>
<td>8.3% (10)</td>
</tr>
<tr>
<td>Cold</td>
<td>25.0% (15)</td>
<td>25.8% (31)</td>
<td>21.7% (26)</td>
<td>8.3% (10)</td>
</tr>
<tr>
<td>Fever</td>
<td>16.7% (10)</td>
<td>20.8% (25)</td>
<td>13.3% (16)</td>
<td>9.2% (11)</td>
</tr>
<tr>
<td>Headache</td>
<td>16.7% (10)</td>
<td>20.0% (24)</td>
<td>10.0% (12)</td>
<td>6.7% (8)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8.3% (5)</td>
<td>16.7% (20)</td>
<td>7.5% (9)</td>
<td>5.8% (7)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>23.3% (14)</td>
<td>14.2% (17)</td>
<td>11.7% (14)</td>
<td>6.7% (8)</td>
</tr>
<tr>
<td>Cough</td>
<td>20.0% (12)</td>
<td>14.2% (17)</td>
<td>10.0% (12)</td>
<td>4.2% (5)</td>
</tr>
<tr>
<td><strong>Most common serious side effects, % (n)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1.7% (1)</td>
<td>7.5% (9)</td>
<td>6.7% (8)</td>
<td>2.5% (3)</td>
</tr>
<tr>
<td>Flu</td>
<td>0% (0)</td>
<td>1.7% (2)</td>
<td>0.8% (1)</td>
<td>0.0% (0)</td>
</tr>
</tbody>
</table>

Based on data collected through September 6, 2019 for Evrysdi 0-12 months and placebo 0-12 months.
Based on data collected through September 30, 2020 for Evrysdi 12-24 months.
Based on data collected through September 6, 2021 for Evrysdi 24-36 months.

*People in the placebo group received placebo for 12 months followed by Evrysdi for 12 months. The Evrysdi period for this group is not shown.

Please see full Prescribing Information for additional Important Safety Information.
Please see full Prescribing Information for additional Important Safety Information.
HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use EVRYSDI safely and effectively. See full prescribing information for EVRYSDI.

EVRYSDI® (risdiplam) for oral solution
Initial U.S. Approval: 2020

-------------------------- RECENT MAJOR CHANGES --------------------------
Indication and Usage (1)  5/2022
Dosage and Administration, Dosing Information (2.2, 2.4)  5/2022

--------------------------- INDICATIONS AND USAGE --------------------------
EVRYSDI is a survival of motor neuron 2 (SMN2) splicing modifier indicated for the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients. (1)

---------------------- DOSAGE AND ADMINISTRATION ----------------------
EVRYSDI must be constituted by a healthcare provider prior to dispensing. Administer orally once daily after a meal using the provided oral syringe. (2.1, 2.4)

<table>
<thead>
<tr>
<th>Age and Body Weight</th>
<th>Recommended Daily Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 2 months of age</td>
<td>0.15 mg/kg</td>
</tr>
<tr>
<td>2 months to less than 2 years of age</td>
<td>0.2 mg/kg</td>
</tr>
<tr>
<td>2 years of age and older weighing less than 20 kg</td>
<td>0.25 mg/kg</td>
</tr>
<tr>
<td>2 years of age and older weighing 20 kg or more</td>
<td>5 mg</td>
</tr>
</tbody>
</table>

See Full Prescribing Information for important preparation and administration instructions. (2.1, 2.4)

--------------------- DOSAGE FORMS AND STRENGTHS ---------------------
For Oral Solution: 60 mg of risdiplam as a powder for constitution to provide 0.75 mg/mL solution. (3)

----------------------- CONTRAINDICATIONS -----------------------
None. (4)

------------------------ ADVERSE REACTIONS ------------------------
The most common adverse reactions in later-onset SMA (incidence at least 10% of patients treated with EVRYSDI and more frequent than control) were fever, diarrhea, and rash. (6.1)
The 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. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------------------- DRUG INTERACTIONS -----------------------
Avoid coadministration with drugs that are substrates of multidrug and toxin extrusion (MATE) transporters. (7.1)

--------------------- USE IN SPECIFIC POPULATIONS ---------------------
Pregnancy: Based on animal data, may cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 3/2023
1 INDICATIONS AND USAGE

EVRYSDI is indicated for the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

Dose Preparation

It is recommended that a healthcare provider discuss with the patient or caregiver how to prepare the prescribed daily dose prior to administration of the first dose [see Instructions for Use].

Instruct patients or caregivers to prepare the dose using the reusable oral syringe provided.

EVRYSDI must be taken immediately after it is drawn up into the oral syringe. If EVRYSDI is not taken within 5 minutes, EVRYSDI should be discarded from the oral syringe, and a new dose should be prepared.

Dose Administration

EVRYSDI is taken orally once daily after a meal at approximately the same time each day.

In infants who are breastfed, EVRYSDI should be administered after breastfeeding. EVRYSDI cannot be mixed with formula or milk.

Instruct patients to drink water after taking EVRYSDI to ensure the drug has been completely swallowed.

If the patient is unable to swallow and has a nasogastric or gastrostomy tube, EVRYSDI can be administered via the tube. The tube should be flushed with water after delivering EVRYSDI [see Instructions for Use].

2.2 Dosing Information

EVRYSDI is administered orally once daily. The recommended dosage is determined by age and body weight (see Table 1).

Table 1 Adult and Pediatric Dosing Regimen by Age and Body Weight

<table>
<thead>
<tr>
<th>Age and Body Weight</th>
<th>Recommended Daily Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 2 months of age</td>
<td>0.15 mg/kg</td>
</tr>
<tr>
<td>2 months to less than 2 years of age</td>
<td>0.2 mg/kg</td>
</tr>
<tr>
<td>2 years of age and older</td>
<td></td>
</tr>
<tr>
<td>weighing less than 20 kg</td>
<td>0.25 mg/kg</td>
</tr>
<tr>
<td>weighing 20 kg or more</td>
<td>5 mg</td>
</tr>
</tbody>
</table>

2.3 Missed Dose

If a dose of EVRYSDI is missed, EVRYSDI should be administered as soon as possible if still within 6 hours of the missed dose, and the usual dosing schedule can be resumed on the next day. Otherwise, the missed dose should be skipped, and the next dose should be taken at the regularly scheduled time on the next day.

If a dose is not fully swallowed or vomiting occurs after taking a dose of EVRYSDI, another dose should not be administered to make up for the lost dose. The patient should wait until the next day to take the next dose at the regularly scheduled time.
2.4 Preparation of Oral Solution by Healthcare Provider

EVRYSDI powder must be constituted to the oral solution by a pharmacist or other healthcare provider prior to dispensing to the patient.

Preparation of the EVRYSDI Oral Solution 0.75 mg/mL

The EVRYSDI “Instructions for Constitution” booklet contains more detailed instructions on the preparation of the oral solution [see Instructions for Constitution].

Caution should be exercised in the handling of EVRYSDI powder for oral solution. Avoid inhalation and direct contact with skin or mucous membranes with the dry powder and the constituted solution. If such contact occurs, wash thoroughly with soap and water; rinse eyes with water. Wear disposable gloves during the preparation and cleanup procedure.

1. Gently tap the bottom of the closed glass bottle to loosen the powder.
2. Remove the cap. Do not throw away the cap.
3. Carefully pour 79 mL of Purified Water into the EVRYSDI bottle to yield the 0.75 mg/mL oral solution. Do not mix EVRYSDI with formula or milk.
4. Insert the Press-In bottle adapter into the bottle opening by pushing it down against the bottle lip. Ensure it is completely pressed against the bottle lip.
5. Re-cap the bottle tightly and shake well for 15 seconds. Wait for 10 minutes. You should have obtained a clear solution. If not, shake well again for another 15 seconds.
6. Write the date of expiration of the constituted oral solution (calculated as 64 days after constitution) and the lot number on the bottle label. Peel off the part of the bottle label that has the expiration date of the powder.
7. Put the bottle back in its original carton.
8. Select the appropriate oral syringes (1 mL, 6 mL, or 12 mL) based on the patient’s dosage and remove the other oral syringes from the carton.
9. Dispense with the “Instructions for Use” and FDA-approved patient labeling. Alert patients to read the important handling information described in the Instructions for Use.

Keep the constituted oral solution of EVRYSDI in the original amber bottle to protect from light. Store in a refrigerator at 2°C to 8°C (36°F to 46°F). Do not freeze. Discard any unused portion 64 days after constitution. Keep the bottle in an upright position with the cap tightly closed.

3 DOSAGE FORMS AND STRENGTHS

EVRYSDI for oral solution: 60 mg as a light yellow, pale yellow, yellow, greyish yellow, greenish yellow, or light green powder for constitution. Following constitution, the volume of the greenish yellow to yellow solution is 80 mL, providing 60 mg/80 mL (0.75 mg/mL) risdiplam.

4 CONTRAINDICATIONS

None.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not reflect the rates observed in practice.
In clinical trials including patients with infantile-onset SMA, later-onset SMA, and pre-symptomatic SMA, a total of 483 patients (50% female, 74% Caucasian) were exposed to EVRYSDI for up to a median duration of 22.8 months (range: 0.5 to 46.9 months), with 221 patients receiving treatment for more than 24 months. At the time of first EVRYSDI dose, 90 (19%) patients were 18 years and older, 119 (25%) were 12 years to less than 18 years, 189 (39%) were 2 years to less than 12 years, 67 (14%) 2 months to less than 2 years, and 18 (4%) were less than 2 months.

**Clinical Trial in Later-Onset SMA**

The safety of EVRYSDI for later-onset SMA is based on data from a randomized, double-blinded, placebo-controlled study (Study 2 Part 2) in patients with SMA Type 2 or 3 (n = 180) [see Clinical Studies (14.2)]. The patient population in Study 2 Part 2 ranged in age from 2 to 25 years at the time of the first dose.

The most common adverse reactions (reported in at least 10% of patients treated with EVRYSDI and at an incidence greater than on placebo) in Study 2 Part 2 were fever, diarrhea, and rash. Table 2 lists the adverse reactions that occurred in at least 5% of patients treated with EVRYSDI and at an incidence ≥ 5% greater than on placebo in Study 2 Part 2.

**Table 2**  Adverse Reactions Reported in ≥ 5% of Patients Treated with EVRYSDI and with an Incidence ≥ 5% Greater Than on Placebo in Study 2 Part 2

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>EVRYSDI (N = 120)</th>
<th>Placebo (N = 60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever¹</td>
<td>22</td>
<td>17</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>17</td>
<td>8</td>
</tr>
<tr>
<td>Rash²</td>
<td>17</td>
<td>2</td>
</tr>
<tr>
<td>Mouth and aphthous ulcers</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Urinary tract infection³</td>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>

¹ Includes pyrexia and hyperpyrexia.
² Includes rash, erythema, rash maculo-papular, rash erythematous, rash papular, dermatitis allergic, and folliculitis.
³ Includes urinary tract infection and cystitis.

**Clinical Trial in Infantile-Onset SMA**

The safety of EVRYSDI therapy for infantile-onset SMA is based on data from an open-label study in 62 patients (Study 1) [see Clinical Studies (14.1)]. The patient population ranged in age from 2 to 7 months at the time of the first EVRYSDI dose (weight range 4.1 to 10.6 kg).

The most frequent adverse reactions reported in infantile-onset SMA patients treated with EVRYSDI in Study 1 were similar to those observed in later-onset SMA patients in Study 2. Additionally, the following adverse reactions reported in ≥ 10% of patients were: upper respiratory tract infection (including nasopharyngitis, rhinitis), lower respiratory tract infection (including pneumonia, bronchitis), constipation, vomiting, and cough.

**Clinical Trial in Pre-Symptomatic SMA**

The safety of EVRYSDI therapy for pre-symptomatic SMA is based on data from an open-label, single-arm study (Study 3) [see Clinical Studies (14.3)]. At the time of interim analysis, the study had enrolled 18 patients with pre-symptomatic SMA between 16 and 40 days of age at the time of the first dose (weight range 3.1 to 5.7 kg). The median exposure duration was 8.7 months.
(range: 0.5 to 22.8 months). The safety profile of EVRYSDI in pre-symptomatic patients in Study 3 is consistent with the safety profile for symptomatic SMA patients treated with EVRYSDI in clinical trials.

7 DRUG INTERACTIONS

7.1 Effect of EVRYSDI on Substrates of Multidrug and Toxin Extrusion (MATE) Protein Transporters

Based on in vitro data, EVRYSDI may increase plasma concentrations of drugs eliminated via MATE1 or MATE2-K [see Clinical Pharmacology (12.3)], such as metformin. Avoid coadministration of EVRYSDI with MATE substrates. If coadministration cannot be avoided, monitor for drug-related toxicities and consider dosage reduction of the coadministered drug (based on the labeling of that drug) if needed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy and fetal/neonatal/infant outcomes in women exposed to EVRYSDI during pregnancy. Physicians are encouraged to register patients and pregnant women are encouraged to register themselves by calling 1-833-760-1098 or visiting https://www.evrysdipregnancyregistry.com.

Risk Summary

There are no adequate data on the developmental risk associated with the use of EVRYSDI in pregnant women. In animal studies, administration of risdiplam during pregnancy or throughout pregnancy and lactation resulted in adverse effects on development (embryofetal mortality, malformations, decreased fetal body weights, and reproductive impairment in offspring) at or above clinically relevant drug exposures [see Data].

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. In the U.S. general population, the estimated background risk of major birth defect and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. Based on animal data, advise pregnant women of the potential risk to the fetus.

Data

Animal Data

Oral administration of risdiplam (0, 1, 3, or 7.5 mg/kg/day) to pregnant rats throughout organogenesis resulted in decreased fetal body weights and increased incidences of fetal structural variations at the highest dose tested, which was not associated with maternal toxicity. The no-effect level for adverse effects on embryofetal development (3 mg/kg/day) was associated with maternal plasma exposure (AUC) approximately 2 times that in humans at the maximum recommended human dose (MRHD) of 5 mg.

Oral administration of risdiplam (0, 1, 4, or 12 mg/kg/day) to pregnant rabbits throughout organogenesis resulted in embryofetal mortality, fetal malformations (hydrocephaly), and structural variations at the highest dose tested, which was associated with maternal toxicity. The no-effect dose for adverse effects on embryofetal development (4 mg/kg/day) was associated with maternal plasma exposure (AUC) approximately 4 times that in humans at the MRHD.

When risdiplam (0, 0.75, 1.5, or 3 mg/kg/day) was orally administered to rats throughout pregnancy and lactation, gestation was prolonged in the dams, and delayed sexual maturation (vaginal opening) and impaired reproductive function (decreased numbers of corpora lutea,
implantation sites, and live embryos) were observed in female offspring at the highest dose. The no-effect dose for adverse effects on pre- and postnatal development in rats (1.5 mg/kg/day) was associated with maternal plasma exposure (AUC) similar to that in humans at the MRHD.

8.2 Lactation

Risk Summary

There are no data on the presence of risdiplam in human milk, the effects on the breastfed infant, or the effects on milk production. Risdiplam was excreted in the milk of lactating rats orally administered risdiplam.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EVRYSDI and any potential adverse effects on the breastfed infant from EVRYSDI or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Studies of risdiplam in juvenile and adult rats and in monkeys demonstrated adverse effects on the reproductive organs, including germ cells, in males at clinically-relevant plasma exposures [see Use in Specific Populations (8.4) and Nonclinical Toxicology (13.1)].

Pregnancy Testing

Pregnancy testing is recommended for females of reproductive potential prior to initiating EVRYSDI [see Use in Specific Populations (8.1)].

Contraception

EVRYSDI may cause embryofetal harm when administered to a pregnant woman [see Use in Specific Populations (8.1)].

Female Patients

Advise female patients of reproductive potential to use effective contraception during treatment with EVRYSDI and for at least 1 month after her last dose.

Infertility

Male Patients

Male fertility may be compromised by treatment with EVRYSDI [see Nonclinical Toxicology (13.1)].

Counsel male patients of reproductive potential receiving EVRYSDI about the potential effects on fertility. Male patients may consider sperm preservation prior to treatment.

8.4 Pediatric Use

The safety and effectiveness of EVRYSDI in pediatric patients (neonates and older) have been established. Use of EVRYSDI for SMA is supported by evidence from adequate and well-controlled studies of EVRYSDI in patients 2 months of age and older with SMA. Use of EVRYSDI for SMA in patients 2 months of age and younger is supported by pharmacokinetic and safety data from pediatric patients 16 days and older, and pharmacokinetic modeling and simulation to identify the dosing regimen [see Clinical Pharmacology (12.3) and Clinical Studies (14)].

Juvenile Animal Toxicity Data

Oral administration of risdiplam (0, 0.75, 1.5, 2.5 mg/kg/day) to young rats from postnatal day (PND) 4 through PND 31 resulted in decreased growth (body weight, tibia length) and delayed sexual maturation in males at the mid and high dose. The skeletal and body weight deficits
persisted after cessation of dosing. Ophthalmic changes consisting of vacuoles in the anterior vitreous were seen at the high dose. Decreases in absolute B lymphocyte counts were observed at all doses after cessation of dosing. Decreases in testis and epididymis weights, which correlated with degeneration of the seminiferous epithelium in the testis, occurred at the mid and high doses; the histopathology findings were reversible, but organ weight persisted after cessation of dosing. Impaired female reproductive performance (decreased mating index, fertility index, and conception rate) was observed at the high dose. A no-effect dose for adverse developmental effects on preweaning rats was not identified. The lowest dose tested (0.75 mg/kg/day) was associated with plasma exposures (AUC) lower than that in humans at the maximum recommended human dose (MRHD) of 5 mg/day.

Oral administration of risdiplam (0, 1, 3, or 7.5 mg/kg/day) to young rats from PND 22 through PND 112 produced a marked increase in micronuclei in the bone marrow, male reproductive organ histopathology (degeneration/necrosis of the seminiferous tubule epithelium, oligo/aspermia in the epididymis, spermatic granulomas), and adverse effects on sperm parameters (decreased sperm concentration and motility, increased sperm morphology abnormalities) at the highest dose tested. Increases in T lymphocytes (total, helper, and cytotoxic) were observed at the mid and high doses. The reproductive and immune effects persisted after cessation of dosing. The no-effect dose (1 mg/kg/day) for adverse effects on postweaning juvenile rats was associated with plasma exposures (AUC) lower than that in humans at the MRHD.

8.5 Geriatric Use

Clinical studies of EVRYSDI did not include patients aged 65 years and older to determine whether they respond differently from younger adult patients.

11 DESCRIPTION

EVRYSDI for oral solution contains risdiplam, which is a survival of motor neuron 2 (SMN2)-directed RNA splicing modifier.

The chemical name of risdiplam is 7-(4,7-diazaspiro[2.5]octan-7-yl)-2-(2,8 dimethylimidazo[1,2-b]pyridazin-6-yl)pyrido-4H-[1,2-a]pyrimidin-4-one. Risdiplam has a molecular weight of 401.46 g/mol.

The molecular formula of risdiplam is C_{22}H_{23}N_{7}O and the chemical structure is shown below.

![Chemical Structure of Risdiplam]

EVRYSDI is supplied as a powder in an amber glass bottle. Each bottle contains 60 mg of risdiplam. The inactive ingredients of EVRYSDI are: ascorbic acid, disodium edetate dihydrate, isomalt, mannitol, polyethylene glycol 6000, sodium benzoate, strawberry flavor, sucralose, and tartaric acid.

The powder is constituted with purified water to yield 60 mg/80 mL (0.75 mg/mL) of risdiplam after constitution [see Dosage and Administration (2.4)].
12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Risdiplam is a survival of motor neuron 2 (SMN2) splicing modifier designed to treat patients with spinal muscular atrophy (SMA) caused by mutations in chromosome 5q that lead to SMN protein deficiency. Using in vitro assays and studies in transgenic animal models of SMA, risdiplam was shown to increase exon 7 inclusion in SMN2 messenger ribonucleic acid (mRNA) transcripts and production of full-length SMN protein in the brain.

In vitro and in vivo data indicate that risdiplam may cause alternative splicing of additional genes, including FOXM1 and MADD. FOXM1 and MADD are thought to be involved in cell cycle regulation and apoptosis, respectively, and have been identified as possible contributors to adverse effects seen in animals.

12.2 Pharmacodynamics

In clinical trials for infantile-onset SMA and later-onset SMA patients, EVRYSDI led to an increase in SMN protein with a greater than 2-fold median change from baseline within 4 weeks of treatment initiation across all SMA types studied. The increase was sustained throughout the treatment period (of at least 24 months).

12.3 Pharmacokinetics

Pharmacokinetics of EVRYSDI have been characterized in healthy adult subjects and in patients with SMA.

After administration of EVRYSDI as an oral solution, pharmacokinetics of risdiplam were approximately linear between 0.6 and 18 mg in a single-ascending-dose study in healthy adult subjects, and between 0.02 and 0.25 mg/kg once daily in a multiple-ascending-dose study in patients with SMA. Following once-daily oral administration of risdiplam in healthy subjects, approximately 3-fold accumulation of peak plasma concentrations ($C_{\text{max}}$) and area under the plasma concentration-time curve ($\text{AUC}_{0-24h}$) was observed. Risdiplam exposures reach steady state 7 to 14 days after once-daily administration.

Absorption

Following oral administration, the time to reach maximum plasma concentration ($T_{\text{max}}$) is between 1 and 4 hours.

Effect of Food

In the clinical efficacy studies (Study 1 and Study 2), risdiplam was administered with a morning meal or after breastfeeding.

Distribution

The apparent volume of distribution at steady state is 190.4 L for a 31.3 kg patient.

Risdiplam is predominantly bound to serum albumin, without any binding to alpha-1 acid glycoprotein, with a free fraction of 11%.

Elimination

The apparent clearance ($\text{CL/F}$) of risdiplam is 2.45 L/h for a 31.3 kg patient. The terminal elimination half-life of risdiplam was approximately 50 hours in healthy adults.

Metabolism

Risdiplam is primarily metabolized by flavin monooxygenase 1 and 3 (FMO1 and FMO3) and also by CYPs 1A1, 2J2, 3A4, and 3A7.
Parent drug was the major component found in plasma, accounting for 83% of drug-related material in circulation. The pharmacologically-inactive metabolite M1 was identified as the major circulating metabolite.

**Excretion**

Following a dose of 18 mg, approximately 53% of the dose (14% unchanged risdiplam) was excreted in the feces and 28% in urine (8% unchanged risdiplam).

**Specific Populations**

There were no clinically significant differences in the pharmacokinetics of EVRYSDI based on race or gender. Renal impairment is not expected to alter the exposures to risdiplam.

The impact of geriatric age on the pharmacokinetics of EVRYSDI has not been studied.

**Hepatic Impairment**

The pharmacokinetics and safety of risdiplam have been studied in subjects with mild or moderate hepatic impairment (as defined by Child-Pugh class A and B, respectively, \( n = 8 \) each) compared to subjects with normal hepatic function \( (n=10) \). Following the administration of 5 mg EVRYSDI, the \( AUC_{\text{inf}} \) and \( C_{\text{max}} \) of risdiplam were approximately 20% and 5% lower, respectively, in subjects with mild hepatic impairment and were approximately 8% and 20% higher, respectively, in subjects with moderate hepatic impairment, versus matched healthy control subjects. The magnitude of these changes is not considered to be clinically meaningful. The pharmacokinetics and safety in patients with severe hepatic impairment (Child-Pugh class C) have not been studied.

**Pediatric Patients**

Body weight and age were found to have significant effect on the pharmacokinetics of risdiplam. The estimated exposure (mean \( AUC_{0-24h} \)) in pre-symptomatic infants at the age of 1 to 2 months was 1920 ng.h/mL at the recommended dose of 0.15 mg/kg once daily. The estimated exposure for infantile-onset SMA patients (age 2 to 7 months at enrollment) at the recommended dose of 0.2 mg/kg once daily was 1930 ng.h/mL. The estimated exposure for later-onset SMA patients (2 to 25 years old at enrollment) at the recommended dose was 2070 ng.h/mL (0.25 mg/kg once daily for patients with a body weight < 20 kg and 5 mg once daily for patients with a body weight \( \geq 20 \) kg).

No data on risdiplam pharmacokinetics are available in patients less than 16 days of age \[\text{see Use in Specific Populations (8.4)}\].

**Drug Interaction Studies**

**Effect of Other Drugs on EVRYSDI**

Coadministration of 200 mg itraconazole (a strong CYP3A inhibitor) twice daily with a single 6 mg oral dose of risdiplam did not have a clinically relevant effect on the pharmacokinetics of risdiplam (11% increase in AUC and 9% decrease in \( C_{\text{max}} \)).

Risdiplam is a weak substrate of human MDR-1 and breast cancer resistant protein (BCRP) transporters in vitro. Human MDR-1 or BCRP inhibitors are not expected to result in a clinically significant increase of risdiplam concentrations.

**Effect of EVRYSDI on Other Drugs**

Risdiplam and its major circulating metabolite M1 did not induce CYP1A2, 2B6, 2C8, 2C9, 2C19, or 3A4 in vitro. Risdiplam and M1 did not inhibit (reversible or time-dependent inhibition) any of the CYP enzymes tested (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6), with the exception of CYP3A in vitro.
EVRYSDI is a weak inhibitor of CYP3A. In healthy adult subjects, administration of EVRYSDI once daily for 2 weeks slightly increased the exposure of midazolam, a sensitive CYP3A substrate (AUC 11%; Cmax 16%); this increase is not considered clinically relevant. Based on physiologically-based pharmacokinetic (PBPK) modeling, a similar increase is expected in children and infants as young as 2 months of age.

In vitro studies have shown that risdiplam and its major metabolite are not significant inhibitors of human MDR1, organic anion-translocating polypeptide (OATP) 1B1, OATP1B3, organic anion transporter 1 and 3 (OAT 1 and 3) transporters, and human organic cation transporter 2 (OCT2), at clinically relevant concentrations. Risdiplam and its metabolite are, however, in vitro inhibitors of the multidrug and toxin extrusion (MATE) 1 and MATE2-K transporters [see Drug Interactions (7.1)].

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

The carcinogenic potential of risdiplam has not been fully evaluated. Risdiplam was not carcinogenic in Tg.rasH2 mice when administered at oral doses of up to 9 mg/kg/day for 26 weeks.

Mutagenesis

Risdiplam was negative in an in vitro Ames assay. In an in vivo combined bone marrow micronucleus and comet assay in rat, risdiplam was clastogenic, as evidenced by an increase in micronuclei in bone marrow, but was negative in the comet assay. A pronounced increase in bone marrow micronuclei was also observed in toxicity studies in adult and juvenile rats [see Use in Specific Populations (8.4)].

Impairment of Fertility

Oral administration of risdiplam to rats for 4 (0, 1, 3, or 9 mg/kg/day) or 26 (0, 1, 3, or 7.5 mg/kg/day) weeks resulted in histopathological effects in the testis (degenerated spermatocytes, degeneration/atrophy of the seminiferous tubules) and epididymis (degeneration/necrosis of ductular epithelium) at the mid and/or high doses. At the high dose in the 26-week study, the testicular lesions persisted to the end of the recovery period, which corresponds, in rat, to approximately one spermatogenic cycle. The no-effect dose for adverse reproductive system effects in adult male rats (1 mg/kg/day) was associated with plasma drug exposures (AUC) similar to that in humans at the maximum recommended human dose (MRHD) of 5 mg/day.

Adverse effects of risdiplam on the testis could not be fully evaluated in the monkey because the majority of monkeys tested were sexually immature. However, oral administration of risdiplam (0, 2, 4, or 6 mg/kg/day) for 2 weeks resulted in histopathological changes in the testis (increases in multinucleate cells, germ cell degeneration) at the highest dose. At the no-effect dose for testicular toxicity in monkeys, plasma exposures were approximately 3 times that in humans at the MRHD.

Oral administration of risdiplam to postweaning juvenile rats resulted in male reproductive toxicity (degeneration/necrosis of the testis seminiferous epithelium with associated oligo/asteregic) in the epididymis and abnormal sperm parameters). The no-effect dose for adverse reproductive effects in postweaning male juvenile rats was associated with plasma exposures approximately 4 times that in humans at the MRHD [see Use in Specific Populations (8.4)].
13.2 Animal Toxicology and/or Pharmacology

Retinal toxicity

Risdiplam-induced functional and structural retinal abnormalities were seen in animal studies. In a 39-week toxicity study in monkeys, oral administration of risdiplam (0, 1.5, 3, or 7.5/5 mg/kg/day; high dose lowered after 4 weeks) produced functional abnormalities on the electroretinogram (ERG) in all mid- and high-dose animals at the earliest examination time (Week 20). These findings were associated with retinal degeneration, detected by optical coherence tomography (OCT), on Week 22, the first examination time. The retinal degeneration, with peripheral photoreceptor loss, was irreversible. A no-effect dose for the retinal findings (1.5 mg/kg/day) was associated with plasma exposures (AUC) similar to that in humans at the maximum recommended human dose (MRHD) of 5 mg.

Effect on Epithelial Tissues

Oral administration of risdiplam to rats and monkeys resulted in histopathological changes in epithelium of the gastrointestinal (GI) tract (apoptosis/single cell necrosis), lamina propria (vacuolation), the exocrine pancreas (single cell necrosis), the skin, tongue, and larynx (parakeratosis/hyperplasia/degeneration) with associated inflammation. The skin and GI epithelial effects were reversible. The no-effect doses for effects on epithelial tissues in rats and monkeys were associated with plasma exposures (AUC) similar to that in humans at the MRHD.

14 CLINICAL STUDIES

The efficacy of EVRYSDI for the treatment of patients with infantile-onset, later-onset, and presymptomatic SMA was evaluated in three clinical studies, Study 1 (NCT02913482) and Study 2 (NCT02908685), and Study 3 (NCT03779334), respectively.

The overall findings of these studies support the effectiveness of EVRYSDI in SMA pediatric and adult patients and appear to support the early initiation of treatment with EVRYSDI.

14.1 Infantile-Onset SMA

Study 1 was an open-label, 2-part study to investigate the efficacy, safety, pharmacokinetics, and pharmacodynamics of EVRYSDI in patients with Type 1 SMA (symptom onset between 28 days and 3 months of age). All patients had genetic confirmation of homozygous deletion or compound heterozygosity predictive of loss of function of the SMN1 gene, and two SMN2 gene copies.

Part 1 of Study 1 was designed as a dose-finding study. Part 2 of Study 1 assessed the safety and efficacy of EVRYSDI at 0.20 mg/kg, the recommended dose determined in Part 1 [see Dosage and Administration (2.4)]. Patients from Part 1 did not take part in Part 2.

A total of 62 patients with symptomatic Type 1 SMA were enrolled in FIREFISH Part 1 (n=21) and Part 2 (n=41), of which 58 patients received the recommended dose. The median age of onset of clinical signs and symptoms was 1.5 months (range: 0.9 to 3.0 months). The median age at enrollment was 5.6 months (range: 2.2 to 6.9 months), and the median time between onset of symptoms and the first dose was 3.7 months (range 1.0 to 6.0 months). Of these patients, 60% were female, 57% were Caucasian, and 29% were Asian. The demographics and baseline disease characteristics were comparable between Part 1 and Part 2 of the study.

Effectiveness was established based on the ability to sit without support for at least 5 seconds (as measured by Item 22 of the Bayley Scales of Infant and Toddler Development – Third Edition (BSID-III) gross motor scale) and on the basis of survival without permanent ventilation. Permanent ventilation was defined as requiring a tracheostomy or more than 21 consecutive days of either non-invasive ventilation (≥ 16 hours per day) or intubation, in the absence of an acute reversible event.
The primary endpoint was the proportion of patients with the ability to sit without support for at least 5 seconds (BSID-III gross motor scale, Item 22) after 12 months of treatment in Part 2; 29% of patients (n=12/41) achieved this milestone.

Other efficacy endpoints of EVRYSDI-treated patients in Study 1 (pooled Part 1 and Part 2) are shown in Table 3.

**Table 3  Key Efficacy Results at Month 12 and Month 24 (Study 1, Parts 1 and Part 2)**

<table>
<thead>
<tr>
<th>Efficacy Endpoints</th>
<th>Proportion of Patients Parts 1 &amp; 2 at Month 12</th>
<th>Proportion of Patients Parts 1 &amp; 2 at Month 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor Function and Development Milestones</td>
<td>N = 58 a</td>
<td></td>
</tr>
<tr>
<td>BSID-III, Item 22: sitting without support for at least 5 seconds</td>
<td>32.8%</td>
<td>60.3%</td>
</tr>
<tr>
<td>Survival and Event-Free Survival</td>
<td>N = 62 b</td>
<td></td>
</tr>
<tr>
<td>Alive without Permanent Ventilation</td>
<td>87.1%</td>
<td>83.8%</td>
</tr>
</tbody>
</table>

a  Results were pooled from all patients who received the recommended dose of risdiplam (all patients in Part 2 and those in the high-dose cohort of Part 1; n=58).
b  Results were pooled from all patients who received any dose of risdiplam in Part 1 and Part 2 (n=62).

At Month 24, 40% (23/58) of patients who received the recommended dose achieved sitting without support for 30 seconds (BSID-III, Item 26). In addition at Month 24, patients continued to achieve additional motor milestones; 28% (16/58) of patients achieved a standing measure (16% [9/58] supporting weight and 12% [7/58] standing with support), as measured by Section 2 of the Hammersmith Infant Neurological Examination (HINE-2) which assesses motor milestones.

The proportion of patients alive without permanent ventilation (event-free survival) was 84% for all patients at Month 24 (Table 3). 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. These results indicate a clinically meaningful deviation from the natural history of untreated infantile-onset SMA. As described in the natural history of untreated infantile-onset SMA, patients would not be expected to attain the ability to sit independently, and no more than 25% of these patients would be expected to survive without permanent ventilation beyond 14 months of age.

**14.2 Later-Onset SMA**

Study 2 was a 2-part, multicenter trial to investigate the efficacy, safety, pharmacokinetics, and pharmacodynamics of EVRYSDI in patients diagnosed with SMA Type 2 or Type 3. Part 1 of Study 2 was dose-finding and exploratory in 51 patients (14% ambulatory). Part 2 was randomized, double-blind, placebo-controlled, and is described below.

The primary endpoint in Study 2 Part 2 was the change from baseline to Month 12 in the Motor Function Measure 32 (MFM32) score. A key secondary endpoint was the proportion of patients with a 3-point or greater change from baseline to Month 12 in the MFM32 total score. The MFM32 measures motor function abilities that relate to daily functions. The total MFM32 score is expressed as a percentage (range: 0 to 100) of the maximum possible score, with higher scores indicating greater motor function. Another key secondary endpoint was the Revised Upper Limb Module (RULM). The RULM is a tool used to assess motor performance of the upper limb in
SMA patients. It tests proximal and distal motor functions of the arm. The total score ranges from 0 (all the items cannot be performed) to 37 (all the activities are achieved fully without any compensatory maneuvers).

Study 2 Part 2 enrolled 180 non-ambulatory patients with Type 2 (71%) or Type 3 (29%) SMA. Patients were randomized 2:1 to receive EVRYSDI at the recommended dosage [see Dosage and Administration (2.2)] or placebo. Randomization was stratified by age group (2 to 5, 6 to 11, 12 to 17, or 18 to 25 years of age).

The median age of patients at the start of treatment was 9.0 years (range 2 to 25), and the median time between onset of initial SMA symptoms and first treatment was 102.6 months (range 1 to 275). Of the 180 patients included in the trial, 51% were female, 67% were Caucasian, and 19% were Asian. At baseline, 67% of patients had scoliosis (32% of them with severe scoliosis). Patients had a mean baseline MFM32 score of 46.1, and RULM score of 20.1. Overall baseline demographic characteristics were reasonably balanced between the treatment groups (EVRYSDI and placebo), with the exception of scoliosis (63% in the EVRYSDI arm vs. 73% in the placebo group).

The primary analysis on the change from baseline in MFM32 total score at Month 12 showed a clinically meaningful and statistically significant difference between patients treated with EVRYSDI and placebo. The results of the primary analysis and key secondary endpoints are shown in Table 4 and Figure 1.

**Table 4 Summary of Efficacy in Patients with Later-Onset SMA at Month 12 of Treatment (Study 2 Part 2)**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>EVRYSDI (N = 120)</th>
<th>Placebo (N = 60)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Endpoint:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline in total MFM32 score at Month 12, LS means (95% CI)</td>
<td>1.36 (0.61, 2.11)</td>
<td>-0.19 (-1.22, 0.84)</td>
</tr>
<tr>
<td>Difference from Placebo, Estimate (95% CI)</td>
<td>1.55 (0.30, 2.81)</td>
<td>0.0156</td>
</tr>
<tr>
<td><strong>Secondary Endpoints:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion of patients with a change from baseline MFM32 total score of 3 or more at Month 12 (95% CI)</td>
<td>38.3% (28.9, 47.6)</td>
<td>23.7% (12.0, 35.4)</td>
</tr>
<tr>
<td>Odds ratio for overall response (95% CI) adjusted (unadjusted) p-value</td>
<td>2.35 (1.01, 5.44)</td>
<td>0.0469 (0.0469)</td>
</tr>
<tr>
<td>Change from baseline in total score of RULM at Month 12, LS means (95% CI)</td>
<td>1.61 (1.00, 2.22)</td>
<td>0.02 (-0.83, 0.87)</td>
</tr>
<tr>
<td>Difference from Placebo, Estimate (95% CI) adjusted (unadjusted) p-value</td>
<td>1.59 (0.55, 2.62)</td>
<td>0.0469 (0.0028)</td>
</tr>
</tbody>
</table>

1. The Mixed Model Repeated Measure (MMRM) analysis included the change from baseline total score as the dependent variable and as independent variables the baseline total score, treatment group, time, treatment-by-time interaction, and the randomization stratification variable of age group (2 to 5, 6 to 11, 12 to 17, 18 to 25).
2. The MFM total score was calculated according to the user manual, expressed as a percentage of the maximum score possible for the scale (i.e., sum of the 32 item scores divided by 96 and multiplied by 100).
3. Based on the missing data rule for MFM32, 6 patients were excluded from the analysis (EVRYSDI n = 115; placebo control n = 59).
4. The adjusted p-value was obtained for the endpoints included in the hierarchical testing and was derived based on all the p-values from endpoints in order of the hierarchy up to the current endpoint.
5. The logistic regression analysis included the baseline total score, treatment and age group as independent variables.
6. Based on the missing data rule for RULM, 3 patients were excluded from the analysis (EVRYSDI n = 119; placebo control n = 58).
14.3 Pre-Symptomatic SMA

Study 3 is an open-label, single-arm, multicenter clinical study to investigate the efficacy, safety, pharmacokinetics, and pharmacodynamics of EVRYSDI in infants up to 6 weeks of age (at first dose) who have been genetically diagnosed with SMA but do not yet present with symptoms.

At the time of an interim analysis, a total of 18 patients with pre-symptomatic SMA were enrolled in Study 3. The efficacy in pre-symptomatic SMA patients was evaluated in 7 patients who had been treated with EVRYSDI for at least 12 months: four patients had 2 copies of the SMN2 gene, 2 patients had 3 copies, and 1 patient had 4 or more copies. Of these 7 patients, the median age at first dose was 35 days (range: 16 to 40 days), 71% were female, 100% were Caucasian.

The 6 patients with 2 or 3 copies of SMN2 achieved the following motor milestones as measured by the HINE-2 at Month 12: 6 (100%) patients achieved sitting (5 patients could pivot/rotate and 1 patient achieved stable sit); 4 (67%) patients could stand (3 patients could stand unaided and 1 patient could stand with support), and 3 (50%) patients could walk independently. All 6 patients were alive at 12 months without permanent ventilation.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Each amber glass bottle of EVRYSDI is packaged with a bottle adapter, two 1 mL reusable oral syringes, two 6 mL reusable oral syringes, and one 12 mL reusable oral syringe. EVRYSDI for
oral solution is a light yellow, pale yellow, yellow, greyish yellow, greenish yellow, or light green powder. Each bottle contains 60 mg of risdiplam (NDC 50242-175-07).

16.2 Storage and Handling

Store the dry powder at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP controlled room temperature]. Keep in the original carton.

Keep the constituted oral solution of EVRYSDI in the original amber bottle to protect from light. Store in a refrigerator at 2°C to 8°C (36°F to 46°F) [see Dosage and Administration (2.4)].

If refrigeration is not available, EVRYSDI can be kept at room temperature up to 40°C (up to 104°F) for a combined total of 5 days. EVRYSDI can be removed from, and returned to, a refrigerator. The total combined time out of refrigeration should not exceed 5 days.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Pregnancy and Fetal Risk

Inform pregnant women and women of reproductive potential that, based on animal studies, EVRYSDI may cause fetal harm [see Use in Specific Populations (8.1)].

Discuss with women of childbearing age whether they are pregnant, might be pregnant, or are trying to become pregnant.

Advise women of childbearing potential to use effective contraception during treatment with EVRYSDI and for at least 1 month after stopping EVRYSDI.

Advise a female patient to immediately inform the prescriber if she is pregnant or planning to become pregnant [see Use in Specific Populations (8.3)].

Pregnancy Registry

Encourage patients to enroll in the EVRYSDI Pregnancy Registry if they become pregnant while taking EVRYSDI [see Use in Specific Populations (8.1)].

Potential Effects on Male Fertility

Advise male patients that their fertility may be compromised while on treatment with EVRYSDI [see Use in Specific Populations (8.3)].

Instructions for Preparation of Oral Solution

Advise patients to ensure that EVRYSDI is in liquid form when received from the pharmacy.

Instruct patients/caregivers to take EVRYSDI after a meal or after breastfeeding at approximately the same time each day. However, instruct caregivers to not mix EVRYSDI with formula or milk.

Instruct patients/caregivers to take EVRYSDI immediately after it is drawn up into the reusable oral syringe [see Dosage and Administration (2.1)].
What is EVRYSDI?
- EVRYSDI is a prescription medicine used to treat spinal muscular atrophy (SMA) in children and adults.

Before taking EVRYSDI, tell your healthcare provider about all of your medical conditions, including if you:
- are pregnant or plan to become pregnant. If you are pregnant, or are planning to become pregnant, ask your healthcare provider for advice before taking this medicine. EVRYSDI may harm your unborn baby.
- are a woman who can become pregnant:
  o Before you start your treatment with EVRYSDI, your healthcare provider may test you for pregnancy. Because EVRYSDI may harm your unborn baby, you and your healthcare provider will decide if taking EVRYSDI is right for you during this time.
  o 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.
  o Pregnancy Registry. There is a pregnancy registry for women who take EVRYSDI during pregnancy. The purpose of this registry is to collect information about the health of the pregnant woman and her baby. If you are pregnant or become pregnant while receiving EVRYSDI, tell your healthcare provider right away. Talk to your healthcare provider about registering with the EVRYSDI Pregnancy Registry. Your healthcare provider can enroll you in this registry or you can enroll by calling 1-833-760-1098 or visiting https://www.evrysdipregnancyregistry.com.
- are an adult male planning to have children: EVRYSDI may affect a man’s ability to have children (fertility). If this is of concern to you, make sure to ask a healthcare provider for advice.
- are breastfeeding or plan to breastfeed. It is not known if EVRYSDI passes into breast milk and may harm your baby. If you plan to breastfeed, discuss with your healthcare provider about the best way to feed your baby while on treatment with EVRYSDI.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Keep a list of them to show your healthcare provider, including your pharmacist, when you get a new medicine.

How should I take EVRYSDI?
See the detailed Instructions for Use that comes with EVRYSDI for information on how to take or give EVRYSDI oral solution.
- You should receive EVRYSDI from the pharmacy as a liquid that can be given by mouth or through a feeding tube. The liquid solution is prepared by your pharmacist or other healthcare provider. 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.

Taking EVRYSDI
- Your healthcare provider will tell you how long you or your child needs to take EVRYSDI. Do not stop treatment with EVRYSDI unless your healthcare provider tells you to.
- For infants and children, your healthcare provider will determine the daily dose of EVRYSDI needed based on your child’s age and weight. For adults, take 5 mg of EVRYSDI daily.
  o Take EVRYSDI exactly as your healthcare provider tells you to take it. Do not change the dose without talking to your healthcare provider.
- Take EVRYSDI 1 time daily after a meal (or after breastfeeding for a child) at approximately the same time each day. Drink water afterwards to make sure EVRYSDI has been completely swallowed.
- Do not mix EVRYSDI with formula or milk.
- If you are unable to swallow and have a nasogastric or gastrostomy tube, EVRYSDI can be given through the tube.
- If you miss a dose of EVRYSDI:
  o If you remember the missed dose within 6 hours of when you normally take EVRYSDI, then take or give the dose. Continue taking EVRYSDI at your usual time the next day.
  o If you remember the missed dose more than 6 hours after you normally take EVRYSDI, skip the missed dose. Take your next dose at your usual time the next day.
If you do not fully swallow the dose, or you vomit after taking a dose, do not take another dose of EVRYSDI to make up for that dose. Wait until the next day to take the next dose at your usual time.

**Reusable Oral Syringes**

- Your pharmacist will provide you with the reusable oral syringe(s) that are needed for taking your medicine and explain how to use them. Wash the syringes per instructions after use. Do not throw them away.
- Use the reusable oral syringe(s) provided by your pharmacist (you should receive 1 or 2 identical oral syringes depending on your prescribed daily dose) to measure your or your child’s dose of EVRYSDI, as they are designed to protect the medicine from light. Contact your healthcare provider or pharmacist if your oral syringe(s) are lost or damaged.
- When transferred from the bottle to the oral syringe, take EVRYSDI right away. Do not store the EVRYSDI solution in the syringe. If EVRYSDI is not taken within 5 minutes of when it is drawn up, EVRYSDI should be thrown away from the reusable oral syringe, and a new dose should be prepared.

What are the possible side effects of EVRYSDI?

The most common side effects of EVRYSDI include:

- **For later-onset SMA:**
  - fever
  - diarrhea
  - rash
- **For infantile-onset SMA:**
  - fever
  - runny nose, sneezing, and sore throat (upper respiratory infection)
  - constipation
  - diarrhea
  - lung infection (lower respiratory infection)
  - vomiting
  - rash
  - cough

These are not all of the possible side effects of EVRYSDI. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store EVRYSDI?

- Store EVRYSDI in the refrigerator between 36°F to 46°F (2°C to 8°C). Do not freeze.
- If necessary, EVRYSDI can be kept at room temperature up to 104°F (up to 40°C) for a combined total of 5 days. EVRYSDI can be removed from, and returned to, a refrigerator. The total combined time out of refrigeration should not be more than 5 days.
- Keep EVRYSDI in an upright position in the original amber bottle to protect from light.
- Throw away (discard) any unused portion of EVRYSDI 64 days after it is mixed by the pharmacist (constitution) or if EVRYSDI has been kept at room temperature (below 104°F [40°C]) for more than a total combined time of 5 days. Discard EVRYSDI if it has been kept above 104°F (40°C). Please see the Discard After date written on the bottle label. (See the Instructions for Use that comes with EVRYSDI.)

Keep EVRYSDI, all medicines and syringes out of the reach of children.

General information about the safe and effective use of EVRYSDI.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use EVRYSDI for a condition for which it was not prescribed. Do not give EVRYSDI to other people, even if they have the same symptoms you have. It may harm them. You can ask your pharmacist or healthcare provider for information about EVRYSDI that is written for health professionals.

What are the ingredients in EVRYSDI?

**Active ingredient:** risdiplam

**Inactive ingredients:** ascorbic acid, disodium edetate dihydrate, isomalt, mannitol, polyethylene glycol 6000, sodium benzoate, strawberry flavor, sucralose, and tartaric acid.

Distributed by: **Genentech, Inc.**, A Member of the Roche Group, 1 DNA Way, South San Francisco, CA 94080-4990

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

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