A Guide to:

# Drug Treatments for Adults in England who have SMA

If you have 5q SMA Type 1, 2 or 3 and are considering the possibility of a drug treatment, you may find this guide useful. It covers questions and topics that you may consider in your discussions with your clinical team.

Though 5q SMA also includes Type 4, the treatments described in these pages are currently only funded by the NHS for Types 1, 2 and 3.

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## 1. Recap of what causes 5q SMA

5q SMA is the most common form of SMA. It's known as '5q SMA' due to its genetic cause.

SMA affects a set of nerve cells called the lower motor neurons, which run from the spinal cord out to our muscles. The lower motor neurons carry messages that make it possible for us to move the muscles that we use to crawl and walk, to move our arms, hands, head, and neck, and to breathe and swallow.

For our lower motor neurons to be healthy, we need to produce an important protein called Survival Motor Neuron (SMN) protein. Most people have two working copies of a gene called *Survival Motor Neuron 1* (*SMN1*)[1], which means they can produce enough SMN protein. People who have 5q SMA have mutations or deletions in both copies of their *SMN1* gene.

Another gene called *SMN2* is sometimes called the 'back-up' gene. It also produces a small amount of SMN protein but, even in healthy people, only makes approximately 10% of the amount produced by *SMN1*.[2] People can have between 0 – 8 copies of the *SMN2* gene.

Having two faulty *SMN1* genes means that an individual relies on the back-up *SMN2* genes and can therefore only produce very low amounts of the SMN protein. This causes the lower motor neurons in their spinal cord to deteriorate and eventually die. Messages from their spinal cord do not efficiently get through to their muscles, making the muscles weak and therefore making movement more difficult or impossible. Their muscles waste due to lack of use and this is known as 'muscular atrophy'.

Having more copies of *SMN2* means that more SMN protein can be made, usually resulting in the impact of the condition being less severe.

**For more information about 5q SMA and its causes:**

**smauk.org.uk/support-information/about-sma**

## 2. Discussions with your clinical team

There are now two treatments funded by NHS England for adults who have 5q SMA, Types 1, 2 or 3. These are:

- **Nusinersen** – the generic name for the drug, trademarked and manufactured by Biogen as **Spinraza™**
- **Risdiplam** – the generic name for the drug, trademarked and manufactured by Roche as **Evrysdi™**

We use both these names in this guide.

Your clinician will check if you already have a genetic report which confirms that you have 5q SMA. If not, they will arrange for you to have a blood test to confirm if your SMA is caused by the mutations or deletions in the *SMN1* genes. Other forms of SMA with different causes would not respond to either of these treatments.

The table and the Q&As that follow summarise information about the treatments. They refer to the criteria for access that have been agreed by NICE (the National Institute for Health and Care Excellence – which assesses whether to recommend a treatment is funded by the NHS in England) and NHS England. The table and Q&As also cover information that you may want to go over with your clinical team as the team and you weigh up the risks and benefits of any treatment that may be possible for you.

The earlier the treatment is started, the greater the effect of the drug is expected to be[3]. This, in turn, suggests that treatment of those with less severe symptoms (*i.e.*, those who have more healthy neurons and muscles) is expected to have the greater effect on outcomes.

For those with very severe muscle weakness, there may not be any measurable response with treatment, but observations that there is no further loss of motor ability or strength (stabilisation) is a benefit in itself as, untreated, SMA is a progressive condition with decline in motor abilities over time. You might want to talk with your clinician about how long it might take to see if your treatment is proving beneficial.

## 3. Summary of Treatments

| Spinraza™ (Nusinersen) | Evrysdi™ (Risdiplam) |
|---|---|
| **Who may have access?** | **Who may have access?** |
| These criteria were based on the information that was known about each drug's clinical and cost effectiveness at the time the recommendations for NHS England funding were made. The information about clinical effectiveness was taken from clinical trials. All treatments require adults to have regular medical and physiotherapy assessments, as discussed further below | |
| Adults who have SMA Type 1, 2 or 3 who:<br>• may have an intrathecal injection (into the spine) in a way that is technically possible and clinically safe<br>• are not permanently ventilated for 16 hours or more a day*<br>• don't have a tracheostomy*<br>• are not receiving Evrysdi™<br>(*Adults who do not meet these criteria but otherwise meet the eligibility criteria would be referred by their clinician for further discussion by, and advice from, the NHS England Clinical Panel) | Adults who have SMA Type 1, 2 or 3 who:<br>• are not permanently ventilated for 16 hours or more a day*<br>• don't have a tracheostomy*<br>• are not receiving Spinraza™<br>(*Adults who do not meet these criteria but otherwise meet the eligibility criteria would be referred by their clinician for further discussion by, and advice from, the NHS England Clinical Panel) |
| **What is it and how does it work?** | **What is it and how does it work?** |
| Spinraza™ is a synthetic antisense oligonucleotide (a small piece of genetic material) that targets the 'back-up' *Survival Motor Neuron 2* (*SMN2*) gene enabling it to produce more functional, full-length SMN protein. | Evrysdi™ is a small molecule drug that targets the 'back-up' *Survival Motor Neuron 2* (*SMN2)* gene and enables it to produce more functional, full-length SMN protein. |
| **How is it given?** | **How is it given?** |
| Spinraza™ is delivered directly into the cerebrospinal fluid (CSF) using a lumbar puncture – a needle is inserted through the skin into the space between the vertebrae (back bones) of the spine. For adults, a local anaesthetic is almost always applied either as a 'numbing cream' or injected under the skin using a very small needle. It is very rare for an adult to need a general anaesthetic for a lumbar puncture. | Evrysdi™ is given in liquid form with a prescribed dose based on a person's weight. It can be given by mouth, nasogastric or gastrostomy tube. Roche's information does not include the possibility of Evrysdi™ by jejunostomy tube. |

| Spinraza™ (Nusinersen) | Evrysdi™ (Risdiplam) |
|---|---|
| **How often is it given?** | **How often is it given?** |
| Spinraza™ injections are given:<br>• On the first day of treatment, day 0; then around day 14; day 28; day 63 - known as 'loading doses'.<br>• Then once every 4 months - referred to as 'maintenance doses'. | Evrysdi™ should be taken once daily after a meal, at approximately the same time each day. It is important not to miss any daily doses. |
| **Where do I have to go to get it?** | **Where do I have to go to get it?** |
| You would need to be assessed at one of the UK's specialist adult neuromuscular centres. Treatment must take place at a hospital. There may be local arrangements as to where treatment and monitoring actually takes place. | You would need to be assessed at one of the UK's specialist adult neuromuscular centres. Once the treatment has been prescribed it can be delivered to your home. It's very important to store risdiplam as instructed in the Patient Information Leaflet. To 'maintain the cold chain' all the bottles must go straight into a fridge and be kept there between doses. |
| **You can find lists of specialist neuromuscular centres at: smauk.org.uk/pb6q** | |
| **How will my response be monitored?** | **How will my response be monitored?** |
| Assessments are carried out approximately once every six months by your clinician and physiotherapist. They use scales that measure how your motor abilities are responding - selecting the ones which are likely to best capture your experience.<br><br>Your feedback is also collected and is referred to as 'Patient Reported Outcome Measures' (PROMs).<br><br>As part of your care, your breathing ability and whether you are needing to have additional ventilatory support will also be monitored. | Assessments are carried out approximately once every six months by your clinician and physiotherapist. They use scales that measure how your motor abilities are responding - selecting the ones which are likely to best capture your experience.<br><br>Your feedback is also collected and is referred to as 'Patient Reported Outcome Measures' (PROMs).<br><br>As part of your care, your breathing ability and whether you are needing to have additional ventilatory support will also be monitored. |

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|---|---|
| **How would I know if the treatment is beneficial?** | **How would I know if the treatment is beneficial?** |
| Treatment is considered beneficial and will continue if:<br>• your condition has stabilised or your motor ability scales show you are making progress *and / or*<br>• whilst on treatment, you haven't become permanently ventilated (defined as 16 hours or more a day for 21 consecutive days in the absence of acute reversible infection or requirement of insertion of permanent tracheostomy). | Treatment is considered beneficial and will continue if:<br>• your condition has stabilised, or your motor ability scales show you are making progress *and / or*<br>• whilst on treatment, you haven't become permanently ventilated (defined as 16 hours or more a day for 21 consecutive days in the absence of acute reversible infection or requirement of insertion of permanent tracheostomy). |
| **How would I know if the treatment isn't beneficial?** | **How would I know if the treatment isn't beneficial?** |
| Treatment may be considered not beneficial if, over two consecutive assessments, your scales show:<br>• your motor abilities are declining *and / or*<br>• whilst on treatment, you have become permanently ventilated (defined as 16 hours or more a day for 21 consecutive days in the absence of acute reversible infection) or requirement of insertion of permanent tracheostomy.<br><br>In all cases, your clinical team would ask for advice from the NHS England national clinical panel of experts as to whether this treatment should continue. Your clinical team would discuss this advice with you. | Treatment may be considered not beneficial if, over two consecutive assessments, your scales show:<br>• your motor abilities are declining *and / or*<br>• whilst on treatment, you have become permanently ventilated (defined as 16 hours or more a day for 21 consecutive days in the absence of acute reversible infection) or requirement of insertion of permanent tracheostomy.<br><br>In all cases, your clinical team would ask for advice from the NHS England national clinical panel of experts as to whether this treatment should continue. Your clinical team would discuss this advice with you. |

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| **What do the clinical trials show?** | **What do the clinical trials show?** |
| There are currently no 'head-to-head' clinical trials or studies that compare the results of these treatments. When you discuss the options with your clinical team, they will not be able to tell you one is better than the other, but will use their knowledge of these trials, 'real world' data and their own experience. Though follow-up data is being collected for **all** drug treatments, uncertainties remain about both the long-term outcomes and the specific outcomes for any individual. | |
| Nusinersen has been tested in clinical trials in humans since 2011.<br><br>It has been consistently shown to have a well understood safety profile and to be well-tolerated in several different trials across 5q SMA populations.<br><br>In many people who have SMA, when compared to placebo or no treatment, nusinersen has been shown to lead to clinically meaningful improvements in muscle function.<br><br>Several trials of nusinersen are currently ongoing.<br><br>You can read more about these clinical trials and their results here: smauk.org.uk/8ono<br><br>Biogen advised us that by the end of March 2022, globally more than 11,000 people have been treated with Spinraza™. | Risdiplam has been tested in clinical trials in humans since 2015.<br><br>It has been consistently shown to have a well understood safety profile and to be well-tolerated in several different trials across 5q SMA populations.<br><br>In many people who have SMA, when compared to placebo or no treatment, risdiplam has been shown to lead to clinically meaningful improvements in muscle function.<br><br>Several trials of risdiplam are currently ongoing.<br><br>You can read more about these clinical trials and their results here: smauk.org.uk/d7my<br><br>Roche advised us that by April 2022, globally more than 5,000 people have been treated with Evrysdi™. |

## What possible side effects can there be with these treatments and what warnings and precautions are given?

Any drug, even ones that are commonly prescribed or sold over the counter, may cause side effects. Side effects of medications must all be noted and reported during their clinical trials. This may mean a side effect is reported that is not directly related to the drug being tested but, for example, is the result of an unconnected infection or illness the patient is experiencing at the time – perhaps one they experience on a regular basis. Side effects are also picked up through the ongoing systems that are in place to monitor medications and their use in the 'real world'. All possible known side effects are always listed in the Patient Information Leaflet or Summary of Product Characteristics that accompany a medication; they are grouped as 'very common' / 'common' / 'uncommon' / 'rare'.

- **The Black Triangle Scheme**

New medicines and vaccines that are under additional monitoring have an inverted black triangle symbol (▼) displayed in their package leaflet and summary of product characteristics, together with a short sentence explaining what the triangle means – it does not mean the medicine is unsafe. Both Evrysdi™ and Spinraza™ are subject to this scheme. If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in the package leaflet. You can also report side effects as follows:

- **The Yellow Card Scheme**

Reporting side effects of medications is hugely important in order to protect people and is everyone's responsibility. This is done via the Yellow Card Scheme which applies to both treatments. If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in the package leaflet. You can also report side effects directly via the Yellow Card Scheme: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. You should also report side effects to the relevant pharmaceutical company.

- **Warnings and Precautions**

These are also described in any Patient Information Leaflet**.**

In the following summary, we describe very common and common side effects for each treatment. We refer to warnings and precautions that clinicians have advised us to highlight. We do not cover rare or very rare side effects or where the frequency of the side effect is not known. We also give you the link to the Patient Information Leaflet for each treatment.

**Your clinical team will discuss warnings, precautions and possible side effects with you before you decide whether to go ahead with treatment. They will arrange for any necessary tests before treatment. They will explain any signs or symptoms you need to look for following treatment. They will also monitor other aspects of your health and wellbeing. You can discuss any questions or concerns you have with your clinician.**

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|---|---|
| **What side effects can it have?** | **What side effects can it have?** |
| Side effects of medications are reported and recorded during their clinical trials. As with most clinical trials, pregnant and breastfeeding women were not included in the trials for Spinraza™ or Evrysdi™. The impact of these medications on a foetus is therefore unknown. If you are planning a pregnancy, talk with your clinician. Side effects are also picked up through the ongoing systems in place to monitor medications and their use in the 'real world'. | |
| Side effects related to the lumbar puncture may occur while nusinersen is being given or afterwards. If experienced, these side effects are expected to occur within 72 hours of the procedure.<br><br>**Very common:** may affect more than 1 in 10 people:<br>• back pain<br>• headache<br>• vomiting | **Very common:** may affect more than 1 in 10 people:<br>• diarrhoea<br>• rash<br>• headache<br>• fever<br><br>**Common:** may affect up to 1 in 10 people:<br>• nausea<br>• mouth sores<br>• bladder infection<br>• joint pain |
| **Warnings and precautions** | **Warnings and precautions** |
| Spinraza™ (and other therapies that work in the same way) can affect:<br>• the levels of platelets in the blood which are necessary for clotting<br>• how well the kidneys work<br><br>For more information, please see the Spinraza™ Patient Information Leaflet:<br><br>**medicines.org.uk/emc/product/2715/pil** | Your clinician will also discuss that contraception for both men and women must be used. Additionally, based on findings in animals, it is advised that Evrysdi™ may reduce male fertility while on treatment and for up to 4 months after the last dose.<br><br>For more information, please see the Evrysdi™ Patient Information Leaflet:<br><br>**medicines.org.uk/emc/product/12582/pil** |
| More information can also be found at:<br><br>**smauk.org.uk/01sf** | More information can also be found at:<br><br>**smauk.org.uk/l32i** |

## 4. Can I have more than one treatment at a time?

No. The NHS doesn't fund more than one treatment at a time.

## 5. Can I switch between treatments?

In January 2022, NICE published guidance on this question (we mostly use NICE's wording[4] in this answer).

Both nusinersen and risdiplam are only available under Managed Access Arrangements (MAAs). An MAA is put in place when a medicine shows promising potential but there is significant uncertainty in the longer-term clinical evidence. MAAs provide a way for people to receive promising new treatments, while further evidence is collected to assess the long-term benefits of a new medicine.

Based on the evidence available when NICE (The National Institute for Health and Care Excellence) made its decisions about recommending risdiplam and nusinersen being funded by the NHS in England, the long-term benefits for people were still very uncertain. The MAAs have been designed to allow enough time for additional evidence to be generated for NICE.

At the end of the MAA period, NICE will consider the new evidence and review whether the medicine should continue to be recommended for use by the NHS. While most treatments recommended for managed access go on to be recommended for routine use on the NHS, there is no guarantee of this.

If people switch between nusinersen and risdiplam, it's likely to be difficult and may not be possible to collect reliable evidence relating to the impact of each individual treatment. As a result, it's possible that the evidence generated under the MAA will be insufficient to enable NICE to recommend one or both drugs for use on the NHS.

Your treating clinician will consider very carefully with you whether there is a clinical reason for you to switch from one treatment (treatment A) to another (treatment B), as switching back to treatment A is only likely to be advisable if:

- treatment B is causing side effects that preclude the administration of treatment B ***and / or***
- there is demonstrable deterioration in motor or respiratory (breathing) function following the switch to treatment B.

Given the complex nature of decisions around switching treatments, the treating clinician will have these discussions face-to-face with you.

It's recommended that treating clinicians seek advice from the **NHS England Clinical Panel** of SMA experts in the event that there may be a case for switching back to treatment A.

Where a switch between treatments is necessary, there should be:

- a gap of four months between stopping treatment with nusinersen and starting treatment with risdiplam

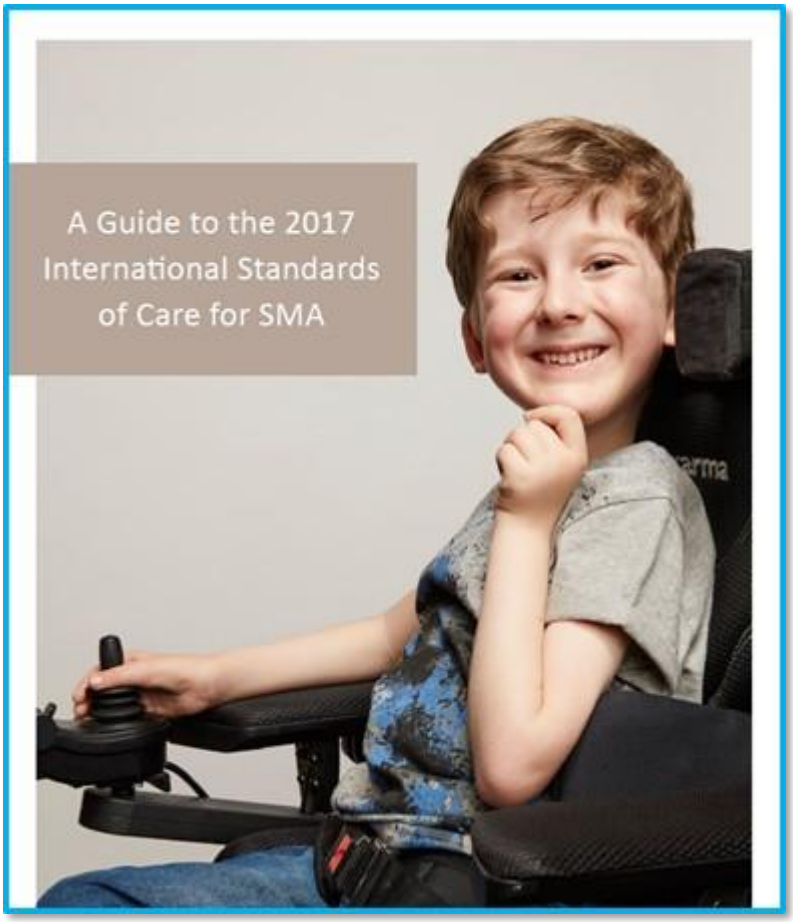
- a gap of 15 days between stopping treatment with risdiplam and starting treatment with nusinersen (this may be shortened exceptionally).

It may be necessary for nusinersen loading doses to be administered again, if you were to switch from nusinersen to risdiplam and then switch back again.

## 6. Is any other care and management needed as well as a drug treatment?

None of the treatments are a cure for 5q SMA and it is essential that you also have the best supportive care possible. This remains important for managing your condition and will help to optimise the impact of the treatment. Care may include breathing support, nutritional support and advice, physiotherapy, spinal and bone care. Important overall everyday advice from clinicians is to 'keep as active as possible and maintain a healthy diet'.

The International Standards of Care for SMA (SoC)[5,6] set out recommendations for all these aspects of care – though it does focus more on children and acknowledges there is more work to be done to achieve guidelines and care standards for adults. There is a family guide[7] to these – see the resources section at the end for the link to this.



## 7. Further Resources

### ➢ SMA UK treatment and research-related information

- This website section tells you about other research developments: smauk.org.uk/treatments-research

- You can keep up to date by signing up for SMA UK's monthly E-news: smauk.org.uk/about/newsletter-sign-up

### ➢ SMA UK condition-related information

- You'll find a wide range of other leaflets and resources in this section of the website: smauk.org.uk/support-information

- Living With SMA has a wide range of information and ideas for daily living: smauk.org.uk/living-with-sma

### ➢ Standards of Care for Spinal Muscular Atrophy (2017)

- You can read or download 'A Guide to the 2017 International Standards of Care for SMA' here: smauk.org.uk/vm4o

## 8. References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7. A Guide to the 2017 International Standards of Care for SMA. Available at: smauk.org.uk/support-information/about-sma/standards-of-care-for-sma (Accessed 18th May 2022)

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***Version 2***
***Author: SMA UK Information Production Team***
***First Published: May 2022***
***Next full review due: May 2025***

*Links last checked: 31st August 2023*

*Our thanks to the writers and reviewers who assist us in our information production. A list of who this includes may be requested from information@smauk.org.uk*

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*Our healthcare information is not intended to replace that provided by your healthcare team. Medical advice for any individual should always come from their own medical team.*

**If you have any feedback about this information, please do let us know at:**
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