Nusinersen (Spinraza™) Treatment for Infants Diagnosed with SMA Type 1

Nusinersen (Spinraza™) is the first drug developed specifically to treat 5q SMA. Decisions from NICE and the Scottish Medicines Consortium mean access to Spinraza treatment through the NHS in the UK is now possible for infants diagnosed with SMA Type 1 for whom treatment is safe and potentially beneficial.

This leaflet aims to provide a summary for parents who want to know more about Spinraza and what treatment could offer, with links to the most up-to-date information we have about UK access and clinical trial results. It is intended to be used in your discussions with your child’s medical team.

For latest information on the possibility of access to this treatment in the UK:

www.smauk.org.uk/uk-access-now
What does nusinersen do? / How does nusinersen work?

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 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 the Survival Motor Neuron (SMN) protein. Our ability to do this is controlled by a gene called Survival Motor Neuron 1 (SMN1). We all have two copies of this gene. Children with SMA have mutations or coding errors in both copies of their SMN1 gene.

Having two faulty SMN1 genes means that a child is only able to produce very low amounts of the SMN protein. This causes their lower motor neurons in their spinal cord to deteriorate. Messages from their spinal cord do not efficiently get through to their muscles, which makes movement difficult. Their muscles waste due to lack of use and this is known as muscular atrophy.

Another gene called SMN2 also helps with the production of SMN protein. As well as having the two faulty SMN1 genes, children with SMA Type 1 have fewer copies of the SMN2 gene so also miss out on this ‘back-up’ source of SMN protein.

Nusinersen is a highly-specialised medicine that can increase the production of SMN protein by targeting the process through which it is produced by the SMN2 gene.

Background to the development of Spinraza?

In collaboration with researchers, nusinersen was developed by Ionis Pharmaceuticals and Biogen Idec. Biogen’s main clinical trials have been with children with SMA Types 1, 2 or 3; there have been no trials with adults or those with SMA Type 4. On 1st June 2017, the European Commission granted nusinersen marketing authorisation under the trade name Spinraza for treatment of those with ‘5qSMA’. Since then, European countries have individually entered into negotiations with Biogen to decide who might be treated under each country’s healthcare system.

For further details of how this progressed in the UK, see: www.smauk.org.uk/uk-access-now

What benefits has nusinersen shown for children with SMA Type 1 in clinical trials?

Biogen’s clinical trial, called ENDEAR, was with 122 children with SMA Type 1 of whom two-thirds were treated with nusinersen and one-third were not treated.

Results for the treated children were:

- 51% improved their motor milestones, compared with 0% not receiving treatment:
22% of infants had head control, 10% could roll over, 8% could sit without support, 1% able to stand, compared with 0% not receiving treatment.

- 61% did not require a ventilator and were still alive, compared with 32% not receiving treatment.

A greater effect was seen in infants receiving nusinersen at an earlier age (the example used was less than around 13.1 weeks).

Clinical trials with other groups of children: those with later onset SMA and pre-symptomatic infants have also been conducted. These results are summarised here: [www.smauk.org.uk/key-clinical-trial-results](http://www.smauk.org.uk/key-clinical-trial-results)

The aim of treatment is to achieve any of these outcomes, but it is not possible to say with any certainty that your child will show improvements.

**How is nusinersen given?**

Nusinersen is delivered directly into the Cerebro Spinal Fluid (CSF). Doctors access the CSF using a lumbar puncture. This is when a needle is inserted through the skin into the space between the vertebrae of the spine (back bones). Doctors may use x-ray to locate the best place for the insertion and they will usually use a local anaesthetic such as ‘numbing cream’, although occasionally a general anaesthetic may be considered necessary. A small amount of CSF is drawn off and then nusinersen is injected over one to three minutes.

Injections are given as follows:

- On the first day of treatment, day 0
- Then around day 14, day 28 and day 63
- Then once every 4 months

**What are the possible side effects of nusinersen?**

As nusinersen is a recently developed medicine, there is no data available about its long-term effects. It has, however, been used in several clinical trials, in which the side effects have been noted:

- **Effects on blood clotting**

  Platelets are important components of the blood which are necessary for clotting of blood. If the platelet level is low, there is a risk of bruising and bleeding or haemorrhage. Nusinersen (and other similar medicines) can affect the levels of platelets in the blood.
Doctors will check platelet levels before starting nusinersen and then at regular points for as long as treatment continues. If the platelet count is low, it may not be safe to go ahead with the administration of nusinersen.

- **Effect on kidney function**

Nusinersen can affect how well the kidneys work, particularly how the tiny filtering units called glomeruli can filter waste products from the blood. Doctors will check kidney function by a blood test and by testing a urine sample before starting nusinersen and then at regular points for as long as treatment continues.

- **Other possibilities**

The following other possibilities were reported during clinical trials, but these may not have been due to the treatment itself; for example, they could have been due to the SMA or an unrelated infection:

- Respiratory symptoms, including breathing difficulties and lung collapse
- Constipation
- Low salt levels
- Skin rash
- High temperature
- Drooling and excess saliva production
- Runny nose

- **Risk of Hydrocephalus**

There have been reports of rare cases of communicating hydrocephalus during treatment with nusinersen; most cases developed after 2 to 4 loading doses\(^5\). From September 2018 healthcare professionals were advised by the UK Medicines and Healthcare products Regulatory Agency (MHRA) to discuss this risk with parents considering the treatment.

**What are the possible side effects of the lumbar puncture procedure?**

There are a number of side effects that can happen due to the procedure rather than the medication. The most frequent are:

- Local pain / discomfort in the back at the site of the lumbar puncture. This should settle within a few days.
- Headache, sometimes with vomiting. This usually settles within a day or two but occasionally can continue for a longer period and need hospital treatment.
Other much rarer complications include:

- **Bleeding** – this is unlikely unless there is a problem such as a low platelet count. If a disorder is identified that predisposes to bleeding advice will be given as to whether it is safe to go ahead.

- **More persistent headaches.** When these symptoms are more persistent, it may be because there is a continuing small leak of the fluid (CSF) and very rarely this can then need treatment to stop the continuing leakage.

Mostly the procedure is carried out without sedation or general anaesthesia. If either of these is required, though healthy individuals usually cope well, there are additional risks for anyone who has a pre-existing medical condition, such as SMA. For instance, if breathing is already affected by SMA, breathing problems may develop. Individuals can also feel and be sick, feel dizzy or seem agitated when coming around from the anaesthetic or sedation. Monitoring by an anaesthetist / medical doctor before, during and after the procedure helps to minimise these risks.

**What are the long-term effects of nusinersen treatment?**

Clinical trials only began in 2011 which means that the longer-term outcomes are not yet known. Nusinersen was, however, given as a treatment in a number of countries to many children with SMA Type 1 via Biogen’s ‘compassionate use’ Expanded Access Programme which closed in the UK in November 2018. Spinraza™ is also available in many countries now via their health systems. You can read summaries of published articles that review treatment outcomes that have been seen in these ‘real world’ studies here: [www.smauk.org.uk/reviews-of-the-eap](http://www.smauk.org.uk/reviews-of-the-eap)

**Is any other intervention needed as well as nusinersen?**

Nusinersen is not a cure for SMA Type 1, it’s a treatment. It’s also not clear how any individual will react to treatment.

In view of this and the complexities of the impact of SMA, it’s vital that anyone who has SMA receives the care and management for the condition outlined in the internationally agreed Standards of Care for SMA. These were reviewed and updated in November 2017. As part of this care, any infant with SMA Type 1, the severest most life-threatening form of SMA would be offered what is called palliative care. This is an active approach to care, aiming to support the physical, emotional, cultural, spiritual and practical needs of the infant and family from the point of diagnosis onwards. The overall aim is to achieve the best quality of life for any child.
What alternatives are there to nusinersen?

Nusinersen is the only treatment currently available. There are other clinical trials of other drugs in the pipeline. If any are happening in the UK, your doctors will discuss possible eligibility with you. Make sure to let your medical team know you would be interested in enrolling your child if they meet the criteria qualify for any that are announced. You can keep up-to-date with developments in research via SMA UK’s website and monthly e-news. Please see contact information at the end of the information sheet.

I may be interested in nusinersen, what should I do now?

Talk to your child’s medical team. If they agree that treatment is safe and potentially beneficial for your child, it is still a very personal decision whether to ask to go ahead. The key thing is to talk everything through and ask any questions you have about:

- Clinical trial results
- What are the results of any ‘real world’ studies
- The possible complications of the treatment and a lumbar puncture

If your child is eligible and you do decide to go ahead, doctors will explain again about the treatment and what it involves. They will also talk with you about what criteria there are for deciding if treatment is working and should continue, or if it should be stopped so that you are clear about this as well. For example, doctors may want to stop treatment if they don’t feel it’s in your child’s best interests, perhaps because their condition has worsened or having repeated lumbar punctures with anaesthesia or sedation is too risky. If this did happen they would discuss this fully with you and make sure other appropriate support and care is in place.

Your medical team will then ask you to record that you understand what they have said and give your permission for treatment. They will talk to you about the plan for when and how this would take place.

You can change your mind at any time, even after you have signed the form consenting to treatment. If you want to withdraw or stop treatment, just discuss this with the doctors, they will completely respect your wishes and ensure other appropriate care and support is in place.
Sources of Support

Your medical team are the best people to talk to about the treatment and about the hospital and community support available to you.

In a more general way, Spinal Muscular Atrophy UK provides free information and support to adults and families in the UK affected by SMA. Our outreach workers can visit you at home. They offer personalised support and information and are available to answer questions. They can discuss with you the support you and your family can access. Please note, we do not give medical advice.

Further Resources

• Biogen’s information about Spinraza™

This can be found here: www.medicines.org.uk/emc/product/2715 Open the tab ‘Patient Leaflet’ for information about the product including any possible side effects. If you open the tab SmPC (Summary of Product Characteristics) you can read their summary of clinical trial result in section 5.1

• SMA UK research-related information:

You will find more information about nusinersen and what is happening in the UK here: www.smauk.org.uk/nusinersen

This website section tells you about other research developments: www.smauk.org.uk/drug-treatments-screening-whats-happening-now

You can keep up to date by signing up for SMA UK’s monthly e-news: www.smauk.org.uk/sign-up-for-mailings

• SMA UK condition-related information

You will find a wide range of other leaflets and resources in this section of the website: www.smauk.org.uk/information

If your child has been recently diagnosed, you may find one of these guides helpful: www.smauk.org.uk/recently-diagnosed-with-sma
Standards of Care for Spinal Muscular Atrophy (2017)

You can read about and download the 2017 internationally agreed Standards of Care from here: www.smauk.org.uk/international-standards-of-care-for-sma

References


We are grateful to the writers and reviewers who assist us in our information production. A list of who this includes may be viewed here: www.smauk.org.uk/our-writers-and-reviewers-panel

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

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