Nusinersen for Children with Spinal Muscular Atrophy Type 1
Information for Families

On 1st June 2017, the European Commission granted nusinersen marketing authorisation under the trade name Spinraza™ for treatment of those with ‘5qSMA’. This refers to a mistake in the SMN1 gene on the fifth chromosome in the chromosomal region labelled ‘q’ which affects those with SMA Types 1, 2, 3 and 4. This is the first treatment ever for SMA to reach this stage.

On 7th May 2018, the Scottish Medicines Consortium announced that it has advised the Scottish NHS that the treatment should be made available to ‘patients with symptomatic type 1 SMA (infantile onset).

In the rest of the UK, the only way to access the treatment is via what is known as the Expanded Access Programme (EAP) for children with SMA Type 1. This programme is only available to children with SMA Type 1 where both the child’s medical team and the child’s parents/guardians have agreed that it could be of potential benefit and that the child is eligible for the treatment.

To help you decide if this is a treatment you want to request for your child, this information sheet explains more about nusinersen and the programme. It then explains what to do if you would like your child to be assessed to join it.

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 / 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.

In collaboration with researchers, nusinersen was developed by Ionis Pharmaceuticals and Biogen Idec.

**What are the benefits of nusinersen?**

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 to 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).

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\(^1\).

**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\(^1\):

- **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 your child’s platelet levels before starting nusinersen and then at regular points for as long as they are receiving treatment. 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 your child’s kidney function. This is checked by a blood test and by testing a urine sample before starting nusinersen and then at regular points for as long as they are receiving treatment.

- **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
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 your child has a problem such as a low platelet count. If your doctor identifies a disorder that predisposes to bleeding they will advise you 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.

You can discuss all these with your medical team before making any decision about going ahead with treatment. You would also have the opportunity to go over them again if you do decide to go ahead.

Mostly the procedure is carried out without sedation or general anaesthesia. If either of these is required, though healthy children usually cope well, there are additional risks in children who have a pre-existing medical condition, such as SMA Type 1. For instance, as breathing may already be affected in SMA Type 1, there is a risk that breathing problems may develop. Children can also feel and be sick, feel dizzy or seem agitated when coming around from the anaesthetic or sedation. An anaesthetist / medical doctor would monitor your child before, during and after the procedure to minimise these risks. Again, you can talk to your medical team about what your child would need for the lumbar puncture before you make any decision and go over this again if you do decide to go ahead.

Will my child only need nusinersen?

Nusinersen is not a cure for SMA Type 1, it is a treatment and, at the moment, it is the only one available.

Because SMA Type 1 is a life-threatening condition and neither the longer-term outcomes of nusinersen treatment is yet known, nor how any individual child will react to treatment, a family would also be offered what is called palliative care. This is an active approach to care, aiming to support the physical, emotional and practical needs of your child and family from the point of diagnosis onwards. It includes the management of symptoms and reducing
complications of muscle weakness following international guidelines as set out in the 2017 International Standards of Care for Spinal Muscular Atrophy. Palliative care also takes into account any cultural and spiritual needs you may have and practical support you need. The overall aim is to achieve the best quality of life for your child.

**What alternatives are there to nusinersen?**

Nusinersen is the only treatment available at the moment. There are other clinical trials of other drugs in the pipeline. If any are happening in the UK, your doctors will discuss these with you and whether your child would be eligible. You can also register with the UK SMA Patient registry which will let you know about any UK trials. You can keep up to date with developments in research via SMA Support UK’s website and monthly e-news. Please see contact information at the end of the information sheet.

There are ‘unknowns’ about both the nusinersen treatment in general and about how your individual child will respond. After talking with your medical team, you may decide this is not the right option for you and your child. This is a very personal decision. Your team will completely respect your wishes and ensure that you and your child receive all the care and support you need from palliative care services.

**What is the EAP for nusinersen?**

It always takes a long time for a new drug that has been observed to be successful in clinical trials to reach the point where it can be given to patients through NHS services. Some pharmaceutical companies therefore offer what is called an Expanded Access Programme (EAP), sometimes called a ‘compassionate use programme’. This is so that patients who did not take part in a clinical trial can access and benefit from the medicine before there is a final decision whether it will be funded by the NHS.

By autumn 2016, the results of Biogen’s ENDEAR clinical trial hadn’t been fully analysed and there was only limited knowledge about the efficacy of nusinersen across the full spectrum of infants and children with SMA Type 1. However, Biogen considered the results to be sufficiently positive for them to work on opening an EAP for children with SMA Type 1 who had not taken part in the trial.

The terms of the EAP for SMA Type 1 are that Biogen supplies nusinersen free of charge to eligible children that their doctors consider would benefit from the medicine. Biogen will ensure that any child that is part of the EAP will continue to receive the drug free for their lifetime. They committed to keep the EAP open in the UK on these terms until the end of 2017. They have subsequently kept the programme open and are likely to continue to do so until England’s National Institute for Health and Care Excellence (NICE) makes its recommendation as to whether the NHS should fund the treatment. This decision is due in November 2018.
Which children are eligible?

To be eligible to join the EAP for SMA Type 1, your child must meet the following criteria:

- Have genetically confirmed 5q SMA
- Have a clinical diagnosis of SMA type 1

In England:

NHS England will provide all hospital costs for administering nusinersen to patients with SMA Type 1 ‘until either the company cease the access scheme to new patients or when the appraisal of the drug has been completed by NICE’.

NHS England will fund children who:

- have onset of clinical signs and symptoms consistent with SMA at ≤6 months (180 days) of age.
- are ≤7 months (210 days) of age at Screening - so will need to have been diagnosed by 7 months of age

There are further criteria your medical team will discuss with you

Children not eligible to take part in the nusinersen EAP include those who:

- are taking part in an ongoing clinical trial of nusinersen, or have taken part in one in the past
- have any brain or spinal cord problem that could make lumbar puncture more difficult or stop the cerebro-spinal fluid (CSF) that surrounds the brain and spinal cord circulating as it should, including presence of a shunt (to drain excess CSF)
- are currently taking part in a gene therapy trial for SMA
- in the six months before the first potential nusinersen dose, have taken part in a programme testing another experimental medicine

For any further updates on eligibility for the administration of nusinersen via the EAP in England, please go to: [www.smasupportuk.org.uk/the-uk-expanded-access-programme-for-nusinersen-for-children-with-sma-type-1](http://www.smasupportuk.org.uk/the-uk-expanded-access-programme-for-nusinersen-for-children-with-sma-type-1)

For eligibility criteria in Wales and Northern Ireland, please check with your medical team.

I’m interested in the EAP for my child, what happens next?

The EAP is not available in all neuromuscular centres in the country but all eligible children should have access at a Centre reasonably local to them. Your medical team will talk with you about whether the EAP is available locally and, if not, where they would arrange for your child to be assessed for eligibility.
Doctors at your local EAP Centre or the one you are referred to will assess your child to make sure that they are eligible to take part. If your child is eligible, doctors will explain again about the nusinersen EAP and what it involves. They will then ask you to record that you understand what they have said and give your permission for your child to take part. They will talk to you about the plan for when and how your child’s treatment would take place. If the EAP is not available locally, your local team will work with NHS England and other Trusts to organise access. There should be no need for you to make contact separately. Doing so can make it more difficult for NHS England and Trusts to keep track of who in the short term needs to go where and to organise the funding for this.

You can change your mind at any time, even after you have signed the form. If you want to withdraw your child from the nusinersen EAP, just tell the doctors caring for your child. Your doctors will completely respect your wishes and ensure other appropriate care and support is in place.

Your doctors may withdraw your child from the nusinersen EAP if they do not feel it is in your child’s best interests, perhaps because your child’s condition has worsened or having repeated lumbar punctures with anaesthesia or sedation is too risky. Again, if this happens, they will ensure you have other appropriate support and care 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 Support UK** provides free information and support to families in the UK affected by SMA. Multisensory toy packs are also available free of charge for babies in the UK diagnosed with SMA Type 1. Our outreach workers are able to 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.

**When will nusinersen be more widely available?**

Nusinersen’s future availability in the UK will depend upon the outcome of reviews by regulatory authorities of the evidence gained from clinical trials in each subtype of SMA. These authorities also review the costs of provision and consider submissions from the patient community. For an update on what stage any reviews have reached and whether the reviews are considering the funding of nusinersen treatment for specific types of 5q SMA only, or for all types of 5q SMA please go to: [www.smasupportuk.org.uk/where-uk-access-has-got-to](http://www.smasupportuk.org.uk/where-uk-access-has-got-to).
Further Resources

- **SMA Support UK research-related information:**

You will find more information about *nusinersen* and what is happening in the UK here: [www.smasupportuk.org.uk/nusinersen](http://www.smasupportuk.org.uk/nusinersen)

This website section tells you about other research developments: [www.smasupportuk.org.uk/drug-treatments-whats-happening-now](http://www.smasupportuk.org.uk/drug-treatments-whats-happening-now)

You can keep up to date by signing up for SMA Support UK’s monthly e-news: [http://smasupportuk.org.uk/sign-up-for-mailings](http://smasupportuk.org.uk/sign-up-for-mailings)

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- **SMA Support UK condition-related information**

You will find a wide range of other leaflets and resources in this section of the website: [www.smasupportuk.org.uk/about-sma](http://www.smasupportuk.org.uk/about-sma)

The leaflets ‘*What is SMA Type 1*’ and ‘*Looking after your baby with SMA Type 1*’ and other information related to SMA Type 1 are in this section: [www.smasupportuk.org.uk/type-1](http://www.smasupportuk.org.uk/type-1)

The **SMA Type 1 route map** can be found at: [www.routemapforsma.org.uk](http://www.routemapforsma.org.uk)

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- **Standards of Care for Spinal Muscular Atrophy (2017)**

You can read about and download the 2017 internationally agreed Standards of Care from here: [http://www.smasupportuk.org.uk/international-standards-of-care-for-sma](http://www.smasupportuk.org.uk/international-standards-of-care-for-sma)

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References


