Healthcare Improvement Scotland | SMC Advice on new medicines

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Patient Group Submission Form

The Scottish Medicines Consortium (SMC) is committed to working in partnership with patient groups to capture patient and carer experiences, and use them to inform decision-making.

Before you make a submission

You are required to complete a patient group partner registration form before you make a submission. The registration form requests general information about your organisation. It only needs to be completed once (and annually updated) and should save you time with any further submissions to SMC. If you have not already completed a registration form, please do this before you make your submission.

You will find it helpful to read our *Guide for Patient Group Partners*, which gives details about the type of information you need to capture in the submission form. **Please read this before you make your submission and use it to help you complete each question.**

You can find the registration form and *Guide for Patient Group Partners* in the Public involvement and Making a submission sections of our website.

Contact us

If you have any more questions after reading the guide, the SMC Public Involvement Team can support you throughout the submission process. You can email us at: his.smcpublicinvolvement@nhs.scot
Please do not hesitate to get in touch, as we are here to help you.

Name of medicine:

Onasemnogene abeparvovec (Zolgensma)

Indication: (what the medicine is used for)

Treatment of 5qSMA

Submission date:

30th November 2020

Name of organisation making submission:

Spinal Muscular Atrophy UK and Muscular Dystrophy UK

Who is the main contact for submissions to SMC?

Name:	Liz Ryburn / Kate Adcock
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Summary of key points

Please summarise the key points of your submission which you would like to emphasise to SMC Committee – bullet points may be helpful.

(See P11 of *A Guide for Patient Group Partners*)

300 words maximum

- SMA Type 1 is a complex and severely disabling condition.
- Best supportive care is outlined in the international Standards of Care for SMA, along with the possibility of nusinersen treatment. This must be regular over a child's lifetime with delivery of nusinersen into the cerebro-spinal fluid via lumbar puncture. Nusinersen does not cross the blood-brain barrier.
- Zolgensma is a ground-breaking 'one off' IV treatment that crosses the blood brain barrier.
- We consider pre-symptomatic access to be very important as the earlier zolgensma treatment, the greater the likelihood of positive outcomes.
- We strongly support access for children classified as SMA Type 1 < 6 months of age.
- In addition, as 5q SMA is a spectrum and zolgensma addresses the genetic cause we hope consideration will be given to widening access to all children diagnosed with 5q SMA who weigh < 13.5 kg and have 2 or 3 *SMN2* copies
- We ask that parents of all children offered zolgensma have the opportunity to discuss with their clinical team:

  o the potential outcome of treatment given their child's age, the time since symptom onset and the impact of their child's SMA

  o how access now would preclude the possibility of future zolgensma treatment being delivered by an alternative method using the same virus
- Neither nusinersen nor zolgensma treatment is a cure and there is no guarantee of the outcome for an individual child. Though the earlier the treatment the better, parents must have as much time as possible during this very distressing time of receiving a diagnosis to have a fully informed confidential discussion with their clinician about the choices open to them. This should include emotional, spiritual, cultural and personal circumstances. Some parents may elect for their child not to have either treatment.

Please provide details of any individuals who have had a significant role in preparing your submission and who have an interest to declare.

(See P11 of *A Guide for Patient Group Partner*s)

300 words maximum

Liz Ryburn, Support Team Manager, Spinal Muscular Atrophy UK

Kate Adcock, Director of Research and Innovation, MDUK

We have no personal conflicts of interest.

Please tell us how you gathered information about the experiences of patients and carers to help inform your submission.

(See P11 of *A Guide for Patient Group Partners*)

300 words maximum

In early 2018, in preparation for our submissions to the SMC and NICE re: the appraisal of nusinersen treatment, SMA UK invited people in the SMA community to complete our on-line surveys.

There were:

- 128 returns describing **the health related impacts of SMA** for 128 people living with SMA Types 1 - 3. Only two of these were from those whose children were affected by SMA Type 1
- 29 returns describing **the experiences of parents whose children had been treated with nusinersen**.

The survey responses were integral to the patient group submissions as part of the evaluation of nusinersen and are here: https://smauk.org.uk/our-surveys-about-the-impact-of-sma-and-views-about-access-to-nusinersen

In July 2019 SMA UK and MDUK conducted a survey asking people within the SMA community for their views on the possibility of the NHS funding onasemnogene abeparvovec (for ease referred to as zolgensma). Disseminated via Patient Groups' social media channels and SMA UK's monthly e-news, this was when many in the SMA community were focused on campaigning

for nusinersen for all with SMA. We were also very aware that parents coping with the distress of a recent diagnosis of SMA Type 1 who had started nusinersen treatment would be very unlikely to want to complete a survey about a treatment that would not be possible for their child. The questionnaire, information sheet and collation of all the 14 responses are here: https://bit.ly/36c255p

This submission draws on: these surveys; the experience and knowledge of SMA UK Support Services Team as a result of its contact over many years with many families affected by SMA; MDUK's Information and Support Team's experience; SMA UK's contact with a small number of families whose children have received Zolgensma treatment. Parents whose children are part of clinical trials were unable to give direct comments that could be reported in this submission. We are therefore only able to quote directly from one parent.

1. How does this condition affect the day-to-day lives of people living with it?

(See P11 of *A Guide for Patient Group Partners*)

500 words maximum

The company has positioned this treatment for infants with SMA Type 1. **We outline the impact of this here but note that SMA is a spectrum –with no clear boundaries between types of SMA.**

Each child is affected differently, but in general, babies with SMA Type 1 are:

- bright, alert and responsive; their intelligence isn't affected
- able to smile and frown as their facial muscles aren't severely affected
- often described as 'floppy' babies due to their low muscle tone (hypotonia) and severe muscle weakness
- unable to support or lift their head due to their weak neck muscles
- unable to sit unsupported and have difficulty rolling over
- able to move their hands and fingers but have difficulty lifting their arms and legs

They have:

- breathing muscle weakness, which can cause a weak cry and difficulties with breathing and coughing
- an increased chance of chest infections, which can be life-threatening
- difficulty swallowing their saliva and other secretions, which may make them sound chesty or make them cough
- difficulties feeding and gaining weight
- an increased risk of fluids or food passing into their lungs (aspiration), which can cause choking and, potentially, chest infections or pneumonia which can quickly become life-threatening.

Impact on Families: The impact of a diagnosis of early onset SMA Type 1 on families is enormous. It often comes as a shock with parents expressing feelings of disbelief, confusion, anger and grief. The 24 hour-a-day responsibility of caring for a child with complex medical needs that follows is physically, emotionally and psychologically exhausting: constant re-positioning and care; large amounts of medical equipment – many families having to adjust bedroom and living arrangements; the need for specialist car seats and buggies that aren't funded by the NHS; frequent hospital appointments and planned and emergency admissions; involvement of palliative and hospice care; caring for other children; the chronic grief and potential looming loss of their child. Parents describe sleep deprivation, often one will give up or cut back their paid work; social lives disappear. Those that have other children and caring responsibilities can struggle to keep up. The genetic implications and emotional and practical impact ripple out to grandparents, other relatives and friends, many of whom will try to help in some way. Caring for a child with SMA Type 1 also comes with significant financial implications

due to the additional costs of living with a disability but also because family members may need to reduce their hours or stop working in order to meet the care needs of the child.

Parents whose children had, in early 2018, begun treatment with nusinersen and responded to our survey that year reflected:

Before treatment:

"he could not even grasp …. he was in intensive care on life support for every cold he got."

"We were told to enjoy our time left with our child at point of diagnosis which was simply heart-breaking. Life as we knew it stopped. Numb with pain and filled with fear we were unable to work/sleep/deal with normal day to day life."

2. How well do medicines which are currently available in NHSScotland help patients manage this condition? (See P12 of *A Guide for Patient Group Partners*)

500 words maximum

The International Standards of Care for SMA (SoC) outline the medications required for **best supportive care** of children who are 'non - sitters':

- Respiratory issues are a leading cause of severe health problems. Medications include ones that can break down secretions, pain relief for pain or distress because of breathlessness, antibiotics for risk of / treatment of a chest infection.
- Swallowing is often unsafe. Medications include those for anti-reflux and to help with constipation. Vitamin D and calcium supplementation may be needed for bone health.
- Albuterol (salbutamol) may be prescribed to help with respiratory muscle strength.

Though these and other proactive interventions described in the SoC help with the management of the condition, they do not treat the underlying causes or halt its progressive nature.

- **Nusinersen**, tested in clinical trials since 2011; available globally since Autumn 2016; approved in Scotland for those with SMA Type 1 in May 2018 and more widely in July 2019 has provided a huge step change as the first drug treatment specifically addressing the cause of SMA. It targets the *SMN2* gene enabling it to produce more functional, full-length SMN protein. Delivered directly into the cerebrospinal fluid (CSF) via lumbar puncture it reaches the motor neurons and other cell types in the spinal cord. As it cannot cross the blood-brain barrier, it may have limited ability to reach other parts of the body. As it doesn't remain in the body long-term, doses must be repeated regularly

for as long as the treating clinician and person/family agree the outcomes are beneficial.

Clinical trial and real-world studies have shown positive results for nusinersen which have been life changing for many children with SMA Type 1 and their families. In general, evidence suggests that early treatment may be necessary to maximise the potential benefits.

In our July 2019 survey, respondents were asked to read accurate information about the administration and clinical trial outcomes of nusinersen and zolgensma and then, score aspects of each one separately. Of the 14 respondents:

- 43% considered the way nusinersen is delivered to be a strong disadvantage / disadvantage
- 64% felt the same with respect to how often nusinersen is delivered
- 7% only thought nusinersen's potential risks and how these are managed were a strong disadvantage / disadvantage
- 71% considered what is known about nusinersen treatment to be a strong advantage / advantage
- 79% considered nusinersen overall to be a totally acceptable / acceptable treatment.

There have been no head to head studies of nusinersen with zolgensma.

3. Have you been able to consult with patients who have used this medicine?

(See P12 of *A Guide for Patient Group Partners*)

Yes ☒ No ☐

4. Would this medicine be expected to improve the patient's quality of life and experience of care, and if so, how?

(See P12 of *A Guide for Patient Group Partners*)

500 words maximum

To date, clinical trial and real-world data show significant positive impacts on children's motor milestones and indicates that early treatment may be necessary to maximise the potential benefits. The hugely positive life changing impact of these outcomes and perhaps more importantly the related impact on children's ability to communicate, their fine motor skills, upper body strength, respiratory and swallowing muscles, fatigue and stamina cannot be stressed enough – and of course the increase in these children's life expectancy. Children would be able to access the world around them, attend nursery and school, join in with the family. They would have fewer - often emergency – hospital admissions for respiratory infections.

One parent was able to tell us about his daughter's experience of zolgensma treatment. In February 2019 at 5.5 months she was given a clinical diagnosis of Type 1C. Access to nusinersen was not possible in England due to the closure of the Expanded Access Programme 3 months previously, so in April 2019, they moved for a period to the USA where she was treated at age 10.5 months. She is now age 2 years 3 months and they are back in the UK:

"Based on our personal experience, we've observed several benefits of the treatment with zolgensma for our daughter. In terms of gains post treatment, she has made huge strides in motor skills and is able to stand independently and take a few steps with support. We continue to see improvements 1.5 years post treatment. She has no issues in terms of respiratory and swallow functions, and her fine motor skills are age-appropriate. Also, compared to nusinersen, which involves repeated lumbar punctures …..she is able to lead a normal life now - with minimal medical intervention."

Zolgensma though is not a cure and over time we may expect children to need equipment, adaptations and assistance in their day to day lives. Although long term treatment outcomes are unknown, we note that children and teenagers who have SMA Type 2 and 3 invariably do well in education and may expect to follow the many adults who have interesting careers and their own families and children. The value of any gains from treatment for their lives is well expressed by another parent with a child age 5 – 12 years with SMA Type 2 who had not been able to access any treatment to date:

"Small improvements in muscle strength have a disproportionately huge impact on quality of life. So, going from not being able to pick up a drink to being able to do this, for example, is a really big deal. Anything that can increase muscle strength will be life changing for children with SMA, and potentially life-saving if it keeps the respiratory muscles a bit stronger.'

5. What kind of impact would treating a patient with this medicine have on the patient's family or carers? (See P13 of *A Guide for Patient Group Partners*)

500 words maximum

Asked to choose one treatment only for an infant newly diagnosed with SMA Type 1 who is well enough and screened as suitable to receive either nusinersen or zolgensma, of our 14 respondents:

- 93% chose zolgensma – including two parents whose children are currently receiving nusinersen treatment;
- 7% chose nusinersen but stated: *'Only because there is more evidence to show it works. If zolgensma had more case studies to relate to I would choose zolgensma'*
- 0% selected to opt for neither and only palliative care and management as outlined in the SoC.

We would therefore expect to see a hugely positive emotional impact on families able to access this treatment and with it the hope it would bring for their child's future. Respiratory and swallowing improvements would mean a reduction in: emergency hospital admissions including time in PICU; the equipment needed for both day and night care – suction, cough assist and NIV; the medications required. No longer a 'non-sitter', the constant need for re-positioning would diminish. Parents may expect to experience less sleep deprivation.

The prospect of a 'one off' treatment compared to ongoing trips to hospital for treatment via lumbar puncture would mean less travelling and disruption to family life and less stress that some children and families experience due to the invasive nature of the treatment. As we have seen with Covid -19, patients and families may wish to avoid hospital visits and interventions in view of their concerns about the risk of infection.

As the above parent whose daughter received zolgensma treatment said:

"Treatment with Zolgensma involves close monitoring for a period of 2-4 months on average. However, beyond this point, there is minimal medical intervention necessary - apart from the various therapies (physiotherapy, occupational therapies). There are no invasive procedures or need to visit hospitals - which has been a great benefit during the time of Covid. We also don't need to take time off work for our daughter's treatment - which means less disruption to our daily life."

It would be very important for families to have in depth discussions with their child's medical team about what they may expect from treatment including understanding the possible impact of factors such as time since diagnosis, disease duration and SMN2 copy numbers. Though not at all easy for a family to take on board (and over time manage), early awareness that their child may, in due course, need: specialised equipment, orthotics, physical therapy and / or orthopaedic surgery to assist with posture and mobility; home adaptations and support with daily living tasks is essential. This will enable them to plan and be prepared if this proves to be the case. The responses we have seen above indicate that families would far rather have this choice and their child remaining in their lives.

6. Are there any disadvantages of the new medicine compared to current standard treatments? (See P13 of *A Guide for Patient Group Partners*)

500 words maximum

In our July 2019 survey, we asked the same questions about zolgensma as nusinersen. Of the 14 respondents:

- 0% considered the way zolgensma is delivered to be a strong disadvantage / disadvantage
- 0% felt the same with respect to how often it is delivered, about its potential risks and how these are managed
- 7% considered what is known about zolgensma treatment to be a strong disadvantage / disadvantage
- 100% considered zolgensma overall to be a totally acceptable / acceptable treatment.

These results are a reasonable reflection of the comments we hear anecdotally from people and are not unexpected.

Safe weight limit: In July 2020, thirteen neuromuscular experts from a variety of countries across Europe, including two from the UK, published a consensus statement about zolgensma treatment advising a safe weight limit of <13.5 kgs: (https://www.ejpn-journal.com/article/S1090-3798(20)30142-2/pdf)

Immunity to the virus: The virus that is packaged with the SMN gene to create zolgensma can be found in the environment; so, some people, including people with SMA, will have a natural immunity to the virus which means the zolgensma therapy as currently delivered will not work for them. Any child being considered for treatment with zolgensma always has a screening blood test to see whether they have this immunity and would therefore not be eligible for the treatment.

Once a child has received this treatment, they develop an immunity to the delivery virus. Clinical trials with older heavier children using the same delivery virus but intrathecally are currently on hold. However, if this were in future a potentially more effective treatment for these children and they had already received it via IV delivery, they would be unable to receive a second treatment. It is important that this is understood by parents, especially if their child is in one of the groups that we highlight in question 7 as potential additional candidates for this treatment.

It is important to note a key advantage of Zolgensma treatment is that it seeks to address the recent evidence that SMN protein is not just found in the spinal cord, it is also present in all cells as soon as an egg is first fertilised. This means that other organs and parts of the body may be affected by a lack of the protein. Unlike nusinersen, zolgensma treatment crosses the blood-brain barrier and therefore can potentially reach many more cell types.

7. Is there any additional information you think may be useful for the SMC committee to consider? (Optional)

500 words maximum

Due to the greater likelihood of positive outcomes, we consider pre-symptomatic access to be very important.

Similarly, we confirm our strong support of the company's application for treatment of children diagnosed with SMA Type 1, aged 6 months or under. However, we would like to have seen the following points considered and a wider application:

Phenotypes

'The clinical classifications and typing….was based primarily on the age of onset and the age of death, with the ability to sit unaided and stand and walk unaided added on. The classifications were never meant as a way to make decisions about who should / should not have access to treatment' (V Dubowitz in 'SMA Disease Mechanisms and Therapy' edited by Summer, Paushkin & Ko, 2016).

A recent large review described the association between SMN2 copy number and SMA phenotype:

- 79% with two copies of *SMN2* developed SMA 1; 5% developed SMA 3
- 54% with three copies of *SMN2* developed SMA 2; 31% developed SMA 3; 16% developed SMA 1.

(Wirth et al Twenty-five years of SMA research: from phenotype to genotype to therapy, and what comes next. Annu. Rev. Genomics Hum Genet 21 231-261 (2020)

Restricting access to those classified as Type 1, when a child with 2 or 3 copies of SMN2 could be classified as Type 1, 2 or 3 risks excluding children:

- not diagnosed in a timely way
  - o parent reports symptoms but is not heard by healthcare professionals
  - o parent has little experience of child development and may miss symptoms
- clinically diagnosed as Type 2 or 3 when this doesn't reliably indicate the future outcome and impact of their SMA:
  - o **child 1** symptoms 7 - 12 months, diagnosed Type 2 - symptoms may have been missed (see above) and / or their SMA may develop to impact more severely than for a 'typical' child diagnosed Type 2 or a child diagnosed Type 1.
  - o **child 2** symptoms 18 months - 3 years, diagnosed Type 3a. The actual trajectory of their SMA may mean they: rapidly lose the ability to walk; develop respiratory symptoms. 95% diagnosed Type 3 with 3 SMN2 copies lose walking ability by their teenager years – with all the emotional and physical impact and long run costs.

We would be pleased to see a wider treatment programme including these children, provided they are within the safe weight limit of < 13.5 kgs.

We also suggest it is desirable to align as far as possible with Europe. Nusinersen showed that narrow indications in some countries set up enormous stress for the global SMA community. Families seek access in countries embracing the wider label. We are alerted almost daily to a new family's crowdfunding effort to fund zolgensma privately - including UK families. This is not the way to deliver treatment and healthcare equitably and safely to children and puts families at huge financial and emotional risk. It also adds uncertainty and potentially hampers coordinated follow-up care.

We also ask for children within the safe weight limit whose parents wish them to switch therapy to be considered, acknowledging the cost and clinical implications.

8. Do you consent for a summary of your submission to be included in the Detailed Advice Document for this medicine?

Yes ☒ No ☐

Thank you for completing this form.

The Public Involvement Team is available to advise you on how to complete this form to ensure the patient and carer experience is fully captured, to help inform the SMC decision making process.
If you have any questions about completing this form, please email it to:
his.smcpublicinvolvement@nhs.scot