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Recommendations concerning the information required to monitor nusinersen use in real-world settings

English summary

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Direction du médicament

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SUMMARY

Introduction

The recognized indication for nusinersen in the treatment of individuals with 5q spinal muscular atrophy (SMA) type I was modified in December 2018 to include presymptomatic individuals and those with type II or III of the disease, provided that clinical monitoring in a real-world setting is carried out. The Institut national d'excellence en santé et en services sociaux (INESSS) considers it necessary to advocate, for targeted drugs, the notion of value promise when if assesses their therapeutic value, in addition to emphasizing the clinical monitoring requirements, in order to ensure equitable and reasonable access to the drugs Quebecers require for their health. The Ministère de la Santé et des Services sociaux asked INESSS to determine the minimum information required to monitor nusinersen use and the minimum frequency at which this information should be gathered for presymptomatic individuals and those with type I, II or III. Ultimately, clinical monitoring will make it possible, among other things, to document the impact of nusinersen on their ability to maintain a functional status deemed clinically meaningful, their quality of life and their life expectancy.

Methods

For the purposes of this request, we gathered data from the scientific literature, contextual information, and experiential knowledge obtained from consultations with stakeholders, SMA patients and caregivers. A literature review was conducted to glean the data that were used in clinical studies to assess the impact of nusinersen on SMA patients' motor function and quality of life. To gather contextual information and experiential knowledge, an advisory committee consisting of health professionals and representatives from the Programme de gestion thérapeutique des médicaments (PGTM) was formed. Consultations with SMA patients and caregivers completed the gathering of experiential knowledge. The Canadian Neuromuscular Disease Registry was consulted as well. Triangulating the data from the scientific literature, the contextual information and the experiential knowledge enabled us to develop preliminary recommendations, which were then submitted to the members of the Comité scientifique d'évaluation des médicaments aux fins d'inscription (CSEMI) for deliberation.

Results

The minimum information required to assess the impact of nusinersen on motor function should be obtained using one or more of the following motor function measurement tools, depending on the patient's age and functional status: the HINE Section 2, the CHOP INTEND (or the CHOP ATEND), the HFMSE, the RULM, or the 6MWT. However, more subtle questioning of the patient or his/her caregiver will be used to record, in the space marked "Other motor skills", information not obtained with one of the recommended measurement tools.

The minimum information required to assess the impact of nusinersen on quality of life should be obtained using the tools PedsQL 4.0 and 3.0 for patients 24 months of age or older, along with the SMAFRS, a measurement tool for assessing functional capacity, and qualitative data on patients' (or a caregiver's) and health professionals' perceptions. The minimum information required to assess the impact of nusinersen on motor function, quality of life, functional capacity, patients' and health professionals' perceptions, and perceptions of respiratory function and of previous or current treatments administered to modify the course of the disease should be gathered at least at the start of treatment and then every 12 months. Additional information regarding quality of life and functional capacity, such as the use of ventilation support or a gastrointestinal tube, scoliosis surgery or, simply, hospitalization, should be gathered every 12 months. Information for documenting the impact of nusinersen on the life expectancy of SMA patients should be gathered using the date of death, if applicable. The nusinersen stop date should also be recorded, if applicable. Information on nusinersen administration and tolerance of this drug should be gathered at each administration. Additional procedures performed during its administration should be recorded at the time of each administration in order to document the organization of care and services. Lastly, information for profiling each nusinersen user should be gathered at the time of the first dose of the drug.

Conclusions

In December 2018, INESSS recommended to the Minister that a recognized indication for nusinersen be added to the *List of Medications – Institutions* for the treatment of children with presymptomatic 5q SMA and that the recognized indication for the treatment of patients with 5q SMA type I be modified to include types II and III of the disease, if its use is guided on a recognized indication that promotes appropriate use, if clinical monitoring is put in place and if the manufacturer helps mitigate the economic burden.

The recommendations in this report are intended to fulfill one of the conditions set out, namely, providing clinical monitoring of patients with SMA 5q of all types. Thus, recommendations aimed at developing an approach to evaluation in a real-world setting have been drawn up. These recommendations concern the minimum information required for documenting the use of nusinersen in a real-world setting, particularly with regard to certain efficacy and safety parameters, and to its administration and the repercussions on the organization of intrahospital services. The frequency at which health-care institutions should share the information and the measures to be taken to implement this clinical monitoring remain to be defined with the Ministère de la Santé et des Services sociaux.

Recommendations concerning the minimum information required to clinically monitor nusinersen use in presymptomatic individuals and in those with 5q SMA type I, II or III in a real-world setting

1. The minimum information required to clinically monitor nusinersen use in presymptomatic individuals and in those with 5q SMA type I, II or III in a real-world setting should be as follows:

   - The impact of nusinersen on motor function should be ascertained by one or more of the six measurement tools, depending on the individual's age and functional status:
     - In children aged 2 to 24 months who are unable to sit up, the Hammersmith Infant Neurological Exam (HINE) Section 2 could be used;
     - In infants and children under 24 months of age, or over 24 months of age who are unable to sit up, the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) could be used;
     - In adults unable to sit up, the Children's Hospital of Philadelphia Adult Test of Neuromuscular Disorders (CHOP ATEND) could be used;
     - In children over 24 months of age who are able to sit up or walk, the Hammersmith Functional Motor Scale Expanded (HFMSE) could be used;
     - In children over 30 months of age and adults who are able to sit up or walk, the Revised Upper Limb Module (RULM) could be used;
     - In children (preferably over 60 months of age) and adults who are able to walk, the 6-Minute Walk Test (6MWT) could be used.
   - The information entered in the space marked "Other motor skills" should be used to document (1) certain subtle changes that might not be detected by the recommended motor skill measurement tools, (2) the results of motor skill assessments done prior to the implementation of INESSS's recommendations that are not in line with these recommendations in terms of the choice of measurement tools, (3) the results of motor skill assessments obtained with measurement tools other than the recommended ones if the health professional observes a floor or ceiling effect;
   - The impact of nusinersen on quality of life should be measured with the following tools: the generic Pediatric Quality of Life Inventory (PedsQL) (4.0) and the neuromuscular disease-specific module (3.0) for patients 24 months of age and older.
   - In adults, the impact of nusinersen on functional capacity should be ascertained using the Spinal Muscular Atrophy Functional Rating Scale (SMAFRS).
   - The following additional information for documenting quality of life and functional capacity should be gathered as well: the use of ventilation support, the use of a gastrointestinal tube, all-cause hospitalizations, scoliosis surgery, and the SMA patient's and a health professional's quality-of-life perceptions.
   - The information on the potential impact of nusinersen on life expectancy should be the date of death, if applicable.
   - The minimum information required on the administration of nusinersen, tolerance of the drug, respiratory function, the previous or current treatments administered to modify the course of the disease, and the additional procedures performed

during its administration should be as follows: the date nusinersen was administered (day/month/year), the nusinersen dose administered (the number of mg per injection, standard or reduced dose, the number of doses), any serious adverse effects related to nusinersen, forced vital capacity (FVC) by spirometry, the cough peak expiratory flow (CPEF) as measured by a peak flow meter, any pharmacological treatments received in clinical trials (the start and stop dates) or rehabilitation services (the start and stop dates), any additional procedures performed during nusinersen administration (anesthesia, radiology, hospital stay [number of days], etc.) and the nusinersen stop date (day/month/year).

- The minimum information required for characterizing each treated patient should be as follows: sex, the date of birth (day/month/year), the type of SMA (type I, II, III or presymptomatic), genetic confirmation of the disease (mutation or absence of the SMN1 gene), the copy number of the SMN2 gene, the age at diagnosis (in months or years), the presence of any symptoms (if applicable, the age at onset of the symptoms in months or years).

Recommendations regarding the minimum frequency at which the minimum information required for clinically monitoring nusinersen use in presymptomatic individuals and in those with 5q SMA type I, II or III in a real-world setting

2. The minimum information required to clinically monitor nusinersen use in presymptomatic individuals and in those with 5q SMA type I, II or III in a real-life setting should be gathered at four frequencies:

   - **At the time of the first administration of nusinersen:** sex, the date of birth (day/month/year), the type of SMA (type I, II, III or presymptomatic), genetic confirmation of the disease (mutation or absence of the SMN1 gene), the copy number of the SMN2 gene, the age at diagnosis (in months or years), the presence of any symptoms (if applicable, the age at onset of the symptoms in months or years).
   - **At the time of each administration of nusinersen:** the date of administration (day/month/year), the dose administered (the number of mg per injection, standard or reduced dose, the number of doses), serious adverse effects related to nusinersen and any additional procedures during administration (anesthesia, radiology, hospital stay [number of days], etc.).
   - **At least when the treatment is initiated and then every 12 months**:
     - Information on the impact of nusinersen on the motor function obtained with one or more of the following measurement tools: the HINE Section 2, the CHOP INTEND (or the CHOP ATEND), the HFMSE, the RULM or the 6MWT;
     - Information on the impact of nusinersen on quality of life and functional capacity obtained with the measurement tools PedsQL 4.0 and 3.0, with data on quality of life as perceived by the patient and a health professional, and with the SMAFRS;
     - Information on respiratory function obtained with the following tests: FVC and the CPEF;
     - Information on previous or current treatments administered to modify the course of the disease.

- **Every 12 months**: the other motor skills, the use of ventilation support, the use of a gastrointestinal tube, all-cause hospitalizations, scoliosis surgery, the nusinersen stop date, and the date of death, if applicable.
- **If applicable:** the nusinersen stop date and the date of death.

Recommendations to be implemented for clinically monitoring nusinersen use in presymptomatic individuals and in those with 5q SMA type I, II or III in a real-world setting

Gathering information

To clinically monitor nusinersen use in presymptomatic individuals and in those with 5q SMA, a standardized form should be created to gather information from patients treated at each health-care facility that administers the drug. The layout of this form remains to be determined, but it should be attachable to the nusinersen-treated patient's medical record. In a second development phase, the form could be standardized and computerized.

For patients treated with nusinersen before the standardized form is implemented, the information could be gathered by archivists. They could complete the standardized form with information entered into the medical records or the records from rehabilitation departments at several institutions.

Data sharing and analysis

The Minister will have to determine who will be given the task of gathering the information using the standardized form, analyzing the data and submitting the results of the follow-up evaluations in the form of reports that preserve the anonymity of nusinersen-treated patients. This task could, for example, be given to a team of researchers working at one of the facilities that uses nusinersen, with the required funding.

The standardized, computerized form created in the second development phase may require the designation of a body where the data would be consolidated and another body that would analyze the data and produce reports. An implementation strategy will need to be developed to support the development of a standardized, computerized form.

Health-care facilities will have to send the standardized form for nusinersen-treated patients to the agreed-upon body at a frequency to be determined. This body or another body, at the Minister's discretion, shall subsequently carry out the data analysis.

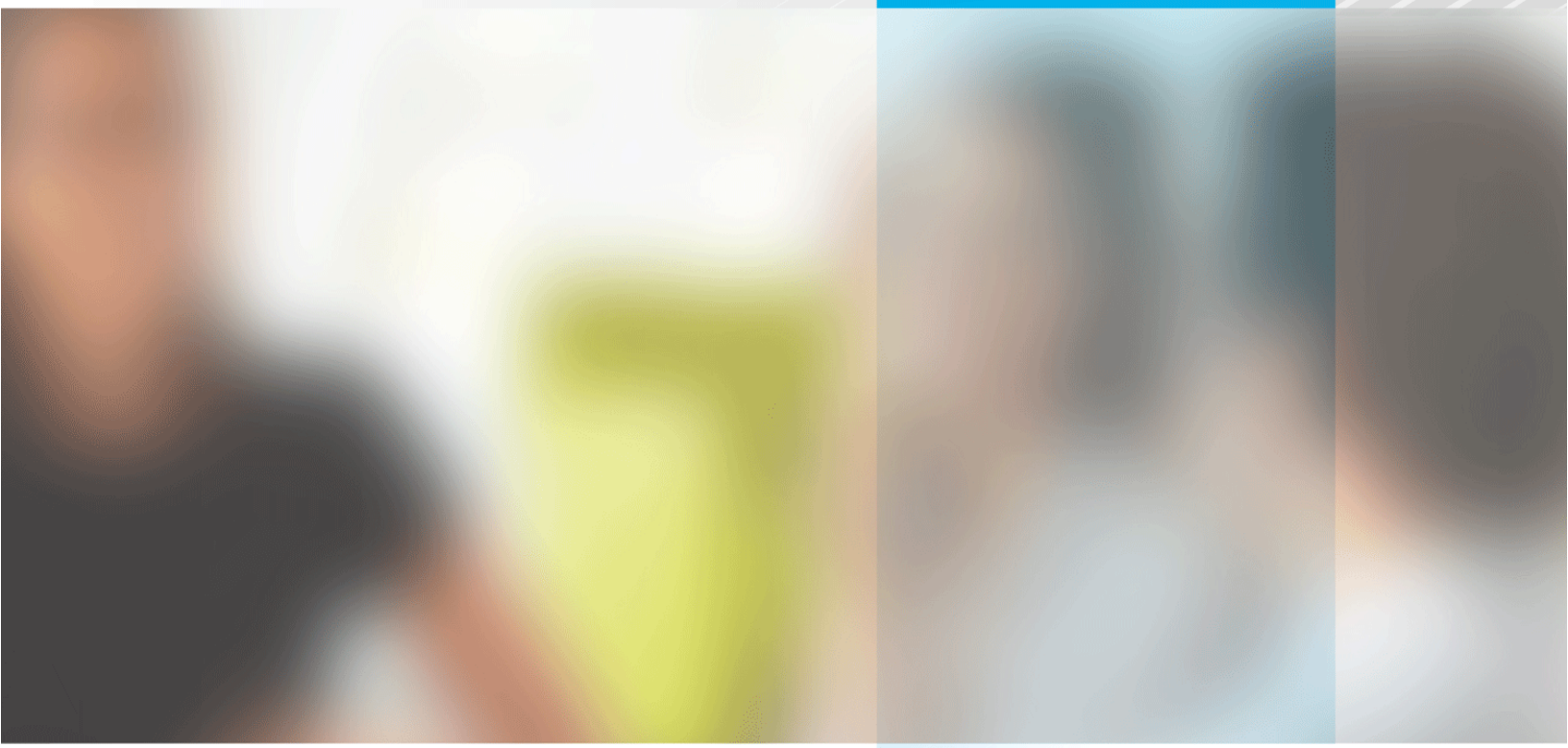
Training

For the purpose of clinically monitoring nusinersen use, the MSSS should ensure that training programs for health professionals aimed at increasing consistency in the assessment of motor function, quality of life and functional capacity using measurement tools are put in place.

The training provided by the manufacturer at health-care facilities on motor function measurement tools will need to be evaluated, if such training is authorized by the MSSS. Regardless of the outcome of this evaluation, training on tools for measuring motor function, quality of life and functional capacity at these facilities will be required.

Literature watch

A literature watch on instruments for measuring motor function or quality of life and functional capacity in SMA patients will be necessary, as they are evolving.



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