Risdiplam

REFUSÉE

Le Comité d'experts, après évaluation, refuse d'inscrire le médicament proposé dans la demande.
La Liste Modèle des Médicaments Essentiels fait état des raisons que les membres du Comité ont identifiées pour refuser l'inscription.

Section: 5. Medicines for diseases of the nervous system

EMLc | Codes ATC: M09AX10

Indication	Spinal muscular atrophy Code ICD11: 8B61.Z
Type de médicament	Chemical agent
Type de liste	Liste de base (EML) (EMLc)
Formulations	Oral > Liquid: 0.75 mg per mL powder for oral liquid
Historique des statuts LME	Demande refusée en 2023 (TRS 1049)
Sexe	Tous
Âge	Aussi recommandé pour les enfants
Équivalence thérapeutique	La recommandation concerne ce médicament spécifique
Renseignements sur le brevet	Main patent is active in several jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org Lire la suite sur les brevets.
Wikipédia	Risdiplam
DrugBank	Risdiplam

Recommandation du comité d'experts

The Expert Committee acknowledged that SMA, a hereditary genetic disease caused by a defect or mutation in the SMN1 gene is associated with considerable morbidity and mortality in affected children and adults. While it has a relatively low incidence in the general population, disease clusters are possible, particularly in families with increased prevalence of consanguinity. The Committee reaffirmed that low incidence of a disease is not a factor on its own that precludes the inclusion of medicines in the Model Lists. Indeed, essential medicines for rare diseases have been included since the first Model List was published (e.g. blood coagulation factors, antirabies hyperimmune serum (later equine rabies immunoglobulin)). The Committee noted the current availability of three different treatments for SMA: one small molecule (risdiplam); one antisense oligonucleotide (nusinersen); and one gene therapy (onasemnogene abeparvovec). These treatments share some characteristics: they are associated with potentially important clinical benefits which appear to be greatest with early introduction of treatment in presymptomatic infants who carry the gene mutation and in symptomatic patients with recent onset of symptoms; and they are all highly priced. Between risdiplam and nusinersen, the Committee noted the feasibility advantages of risdiplam over nusinersen. The latter requires an intrathecal injection every 4 months which must be done in hospital by trained health professionals and has adverse effects such as headaches, vomiting, back pain and risk of infections, while risdiplam is given orally at home. The Committee noted that the body of evidence for efficacy and safety of risdiplam in SMA was still limited, with only a small number of patients exposed to long-term treatment. The Committee noted that most patients had a disease duration of at least 3 months when they were enrolled in the clinical trials. About 50% of children treated with risdiplam showed improvement in motor function (e.g. sitting without support for 5 or more seconds) at 24 months, and more children achieved motor milestones with prolonged treatment. While risdiplam is likely associated with longer survival without requirement for permanent mechanical ventilation, based on the available data so far, no participants could stand or walk alone when risdiplam has been given after disease onset. The Committee noted that based on the

available evidence in patients with symptomatic disease, improvements in motor function were observed in younger children (younger than 5 years) but that these improvements became increasingly less noticeable in older children, adolescents and adults. Treatment-related adverse effects were generally mild. Overall, the Committee considered that the magnitude and long-term duration of benefits and potential harms of risdiplam were still uncertain. The Committee noted that newborn screening for SMA has been introduced into routine screening panels in some high-income countries in recent years. However, the effectiveness of such screening programmes in identifying potential patients in a presymptomatic stage of the disease has not yet been assessed. The Committee also noted the preliminary results of ongoing clinical trials of risdiplam in presymptomatic infants up to 6 weeks of age. As risdiplam is likely to be associated with larger benefits when treatment is started before symptom onset, the Committee considered that it would be important to study its long-term effectiveness in those settings where routine newborn screening programmes for SMA are implemented. The Committee advised that data on SMA screening programmes and use of risdiplam in presymptomatic infants should be reviewed as they become available, as well as longer term trial clinical outcomes for use of risdiplam in older, less severely affected, symptomatic patients. The Committee noted the current high price of risdiplam and that reimbursement decisions in some high-income countries have been made subject to managed entry arrangements or price reductions. Generic versions of risdiplam are not currently available. The Committee also noted that a request made by Knowledge Ecology International for a voluntary licence to manufacture and sell a generic version of risdiplam had not been granted by the patent holder. Nevertheless, the Committee considered that risdiplam could be flagged to the Medicines Patent Pool as a potential candidate for negotiating public health-oriented licences, to facilitate affordable access in low- and middle-income countries. Based on these considerations, the Expert Committee did not recommend inclusion of risdiplam on the core list of the EML and EMLc for treatment of spinal muscular atrophy.

Contexte

Risdiplam has not previously been considered for inclusion on the Model Lists. There are currently no treatments for SMA included on the EML or EMLc.

Pertinence pour la santé publique

SMA is a hereditary genetic disease caused by a mutation in the survival motor neuron (SMN1) gene resulting in insufficient levels of survival motor neuron protein. Signs of SMA include muscle weakness and hypotonia, motor difficulties, loss of motor skills, proximal muscle weakness, hyporeflexia, tongue fasciculations and signs of low motor neuron disease (1). Estimates of the incidence of SMA vary from 1 in 6000 to 1 in 12 000 live births (2, 3). The data and research on the incidence of SMA is predominately from Europe and North America. However, the few studies conducted in low- and middle-income countries have reported similar birth incidence with fewer cases surviving the first year of life (4). Five types of SMA exist, which are classified by age at onset of symptoms. Type 0 is usually identified in utero because of a decrease or loss of fetal movement and infants born with SMA type 0 have survival of under 6 months. Type 1 develops in babies younger than 6 months, and this type is the leading genetic cause of death in early infancy (5). Type 2 clinically manifests between 7 and 18 months, type 3 develops after 18 months, and type 4 develops in adulthood and usually causes mild problems (1). Patients diagnosed with SMA exhibit a wide range of motor function, from extremely weak infants unable to sit to adults who can play sport (3). Clinically meaningful treatment outcomes for infants and children are achieving motor milestones, improvement or stabilization of motor and respiratory function, ventilation-free survival and overall survival. For adults, stabilization of motor function and respiratory function, maintaining independence, fewer hospital visits and health-related quality of life are meaningful treatment outcomes (6). Risdiplam is the first oral treatment for SMA. There are currently two other disease-modifying therapies to treat SMA. Nusinersen is an SMN2 targeting antisense oligonucleotide administered by intrathecal injection. Onasemnogene abeparvovec is a gene therapy using a recombinant adeno-associated viral vector containing DNA encoding the normal SMN1 gene administered through a one-time intravenous infusion. Unlike the alternatives, risdiplam treatment does not require hospitalization for administration.

Bénéfices

No systematic reviews or meta-analyses involving risdiplam have been done nor any direct head-to-head studies comparing risdiplam with the two other treatments for SMA. As such, the only studies comparing risdiplam with nusinersen and/or onasemnogene abeparvovec are indirect treatment comparisons. The main clinical trials and indirect comparisons are summarized below. Risdiplam has been evaluated in three clinical trials. FIREFISH examined risdiplam for type 1 SMA in infants (28 days to 7

months), SUNFISH examined risdiplam for type 2/3 non-ambulant SMA in children and young adults (2 to 25 years) and RAINBOWFISH evaluated risdiplam in genetically diagnosed, presymptomatic infants (birth to 6 weeks). FIREFISH and SUNFISH each had two parts: a dose-finding exploratory phase II trial, and a phase III trial testing efficacy and safety. In FIREFISH part 1, 21 patients were enrolled. Their baseline characteristics were consistent with symptomatic patients with type 1 SMA. The median age at enrolment was 6.7 months (range: 3.3–6.9 months) and the median time between onset of symptoms and the first dose was 4.0 months (range: 2.0–5.8 months). A total of 17 patients received the therapeutic dose of risdiplam (the dose selected for part 2). After 12 months of treatment, 41% (7/17) of these patients were able to sit independently for at least 5 seconds. After 24 months of treatment, three more patients receiving the therapeutic dose were able to sit independently for at least 5 seconds, leading to a total of 59% (10/17) achieving this motor milestone (7). In FIREFISH part 2, 41 patients with type 1 SMA were enrolled. The median age at onset of clinical signs and symptoms of type 1 SMA was 1.5 months (range: 1.0–3.0 months), 54% were females, 54% were described as Caucasian and 34% as Asian. The median age at enrolment was 5.3 months (range: 2.2–6.9 months) and the median time between onset of symptoms and the first dose was 3.4 months (range: 1.0–6.0 months). At baseline, the median score on the Children's Hospital of Philadelphia Infant Test for Neuromuscular Disease (CHOP-INTEND) was 22.0 points (range: 8.0–37.0 – possible scores ranged from 0 to 64 with lower scores indicating more severe disease) and the median Hammersmith Infant Neurological Examination Module 2 (HINE-2) score was 1.0 (range: 0.0–5.0 – possible scores ranged from 0 to 26 with lower scores indicating more severe disease). At month 24, 44% (18/41) (90% confidence interval (CI) 31% to 58%) of patients achieved sitting without support for 30 seconds. Patients continued to achieve additional motor milestones as measured by the Bayley Scales of Infant and Toddler Development–third edition (BSID-III): 85% (35/41) were able to roll (8). In a pooled efficacy analysis of FIREFISH part 1 and part 2 outcomes based on the patients treated with the recommended dose, 28% (16/58) of patients achieved the ability to stand as measured by HINE-2. Despite the progress described, no infants achieved independent standing or walking, as assessed by the BSID-III gross motor subscale (9). RAINBOWFISH was an open-label, single-arm, multicentre clinical study to investigate the efficacy, safety, pharmacokinetics and pharmacodynamics of risdiplam in infants up to 6 weeks of age who had been genetically diagnosed with SMA but had not presented any symptoms (10). The primary analysis was conducted at 12 months in six infants with two or three SMN2 copies. The primary endpoint was the proportion of infants sitting without support for 5 or more seconds. Efficacy data from the study indicated that the infants reached a sufficient CHOP-INTEND score: six (100%) infants were able to sit without support, four (67%) were able to stand and three (50%) were able to walk independently. In addition, the infants maintained their swallowing and feeding abilities. Thus far, the study has shown that, after 12 months of treatment with risdiplam, most presymptomatic infants met key milestones. SUNFISH was conducted in non-ambulant patients with types 2 and 3 SMA aged from 2 to 25 years. Part 1 of SUNFISH was dose-finding and exploratory. Part 2 was a multicentre trial to investigate the efficacy, safety, pharmacokinetics and pharmacodynamics of risdiplam. In SUNFISH Part 1, 51 patients were enrolled. Exploratory efficacy analyses showed improvements in motor function scores after 24 months of treatment with mean increases from baseline in the 32-item Motor Function Measure (MFM32) total score (2.7 points, 95% CI 1.2 to 4.2, n = 44), Revised Upper Limb Module total score (2.5 points, 95% CI 1.5 to 3.4, n = 51) and Hammersmith Functional Motor Scale–Expanded total score (0.6 points, 95% CI –0.6 to 1.8, n = 51). Younger patients (2–11 years) achieved greater improvements in motor function than older patients (12–25 years) (11). SUNFISH part 2 is a randomized, placebo-controlled, double-blind study of 180 non-ambulant patients with type 2 (128 patients, 71%) or type 3 (52 patients, 29%) SMA (12). Patients were randomized 2:1 to receive either a therapeutic dose of risdiplam or placebo. Randomization was stratified by age group. The primary endpoint was change from baseline in the 32-item MFM-32 score at month 12. MFM-32 has a possible range of scores from 0 (severe functional impairment) to 100 (no functional impairment). Patients in SUNFISH part 2 had a mean baseline MFM-32 score of 46.1. The baseline demographic characteristics were balanced between risdiplam and placebo arms except for scoliosis (63% of patients in the risdiplam arm and 73% of patients in the placebo control). At 12 months, the least squares mean change from baseline in MFM-32 scores in the risdiplam and placebo groups were 1.36 (95% CI 0.61 to 2.11) and –0.19 (95% CI –1.22 to 0.84), respectively, and a treatment difference of 1.55 points (95% CI 0.30 to 2.81, P = 0·016) favouring risdiplam. This difference is encouraging, particularly if progress is going to be maintained over time. Indirect comparisons Risdiplam and nusinersen Three studies explored indirect comparisons with nusinersen. The first qualitative comparison of treatment between risdiplam and nusinersen concluded that both medicines have had a substantial positive impact on the quality of life of patients with SMA (13). The second study, (funded by the manufacturer of risdiplam) concluded that risdiplam may be superior to nusinersen with regard to survival and motor function in patients with type 1 SMA. The comparison reported a lower likelihood of serious adverse events with risdiplam compared with intrathecally injected nusinersen. The authors noted that the lower likelihood of serious adverse events may also be associated with better efficacy for risdiplam, as there could be some collinearity between motor function and severe adverse events. Comparing risdiplam with

nusinersen in types 2 or 3 SMA was challenging due to the large differences in population. As a result, the study could not draw concrete conclusions from indirect comparisons with types 2 and 3 SMA (14). The third indirect comparison was conducted by the German Institute for Quality and Efficiency in Health Care. The agency concluded that there was no evidence of differences in efficacy between risdiplam and nusinersen, with the exception of long-term ventilation that might be necessary less often with risdiplam (15). Risdiplam and onasemnogene abeparvovec Two studies indirectly compared risdiplam and onasemnogene abeparvovec and found mixed results. One study found that treatment with onasemnogene abeparvovec compared with risdiplam was associated with greater improvement in CHOP-INTEND scores. However, the study cohorts were not fully matched for their disease severity and age (16). The second study was an indirect comparison by the manufacturer of risdiplam which found insufficient evidence to draw conclusions on the relative efficacy of the two treatments because of the substantial differences in study populations (14).

Torts

The safety of risdiplam in treatment of later-onset SMA was evaluated in the SUNFISH part 2 study (12). The most common adverse events were fever, diarrhoea and rash, reported in less than 10% of the patients that received risdiplam. Adverse events that occurred in at least 5% of patients treated with risdiplam and at an incidence of ≥ 5 percentage points higher than placebo included fever (22% versus 17%), diarrhoea (17% versus 8%), rash (17% versus 2%), mouth and aphthous ulcers (7% versus 0%), arthralgia (5% versus 0%) and urinary tract infection (5% versus 0%). The safety of risdiplam in infantile-onset SMA was evaluated in the FIREFISH study (parts 1 and 2) (7,8). The most frequent adverse reactions reported were similar to those reported in later-onset SMA patients. In addition, in FIREFISH part 2, 54% of infants experienced upper respiratory tract infections. Serious adverse events were reported in 68% of patients, with the most frequently reported serious adverse event being pneumonia, a frequent complication due to the SMA itself (e.g. because of bronchoaspiration) which might lead to death. The safety of risdiplam in presymptomatic infants with genetically diagnosed SMA was evaluated in the RAINBOWFISH study (10). No treatment-related serious adverse events were reported in infants treated for ≤ 22.8 months.

Rapport coût/efficacité

All three available treatments for SMA are currently very costly. The application described health technology assessments and reimbursement considerations of risdiplam made by health technology assessment agencies in Canada (6,17), Ireland (18), the Kingdom of the Netherlands (19) and the United Kingdom (20). Overall, health technology assessment agencies found cost–effectiveness analyses difficult to conduct due to the limited number of studies comparing the efficacy of risdiplam with nusinersen or onasemnogene abeparvovec. In some settings, risdiplam was recommended for reimbursement subject to conditions such as price reductions or managed entry arrangements. In others, risdiplam was not recommended for reimbursement until the cost–effectiveness relative to the alternative treatments was improved. A cost–effectiveness study comparing risdiplam and nusinersen for the treatment of SMA type 1 patients in China reported risdiplam to be dominant over nusinersen, with increased quality-adjusted life years and lower costs (21). Table 6 (refer TRS 1049) reports a cost comparison of risdiplam, nusinersen and onasemnogene abeparvovec provided in the application. The application highlights that the most important component of the manufacturing cost of the medicine is the cost of the active pharmaceutical ingredient. The prices of the active pharmaceutical ingredient depend upon manufacturing methods, the scale of production and the extent of competition among suppliers. The current price of risdiplam per unit of active pharmaceutical ingredient in high-income countries ranges from US$ 118 to US$ 209 million per kg. According to the applicant, in a competitive market, manufacturing costs for risdiplam active pharmaceutical ingredient per kg could be as low as US$ 4000 to US$ 40 000, depending on the production scale.

Directives de l'OMS

WHO guidelines for treatment of SMA are not available.

Disponibilité

As of December 2022, risdiplam was approved in 81 countries. Marketing authorization has been filed in several additional countries. Currently, there are no generic manufacturers, nor existing or planned licensing agreements between the patent holder (Roche) and generic manufacturers. A request by Knowledge Ecology International for a voluntary licence to manufacture and sell a generic version of risdiplam was not granted by Roche. Roche has offered access programmes in some lower-income countries to

make risdiplam more affordable.

Autres considérations

In about 10 high-income countries, universal newborn screening programmes now include screening for SMA to identify infants with possible mutations of the SMN1 gene, allowing presymptomatic infants to be treated before the loss of motor neurons, with the goal of achieving improved clinical outcomes (22). This number is likely to increase over the next few years.

1. Spinal muscular atrophy [internet]. Bethseda, MD: National Institute of Neurological Disorders and Stroke, 2023 (https://www.ninds.nih.gov/health-information/disorders/spinal-muscular-atrophy, accessed 6 October 2023).
2. Verhaart IEC, Robertson A, Leary R, McMacken G, König K, Kirschner J, et al. A multi-source approach to determine SMA incidence and research ready population. J Neurol. 2017;264(7):1465–73.
3. D'Amico A, Mercuri E, Tiziano FD, Bertini E. Spinal muscular atrophy. Orphanet J Rare Dis. 2011;6(1):71.
4. Global, regional, and national burden of motor neuron diseases 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2018;17(12):1083–97.
5. Chaytow H, Faller KME, Huang Y-T, Gillingwater TH. Spinal muscular atrophy: from approved therapies to future therapeutic targets for personalized medicine. Cell Reports Medicine. 2021;2(7):100346.
6. Canadian Agency for Drugs and Technologies in Health. CADTH reimbursement review. Risdiplam (Evrysdi). Can J Health Technol. 2021;1(11):205.
7. Baranello G, Darras BT, Day JW, Deconinck N, Klein A, Masson R, et al. Risdiplam in type 1 spinal muscular atrophy. N Engl J Med. 2021;384(10):915–23.
8. Masson R, Mazurkiewicz-Bełdzińska M, Rose K, Servais L, Xiong H, Zanoteli E, et al. Safety and efficacy of risdiplam in patients with type 1 spinal muscular atrophy (FIREFISH part 2): secondary analyses from an open-label trial. Lancet Neurol. 2022;21(12):1110–9.
9. Darras BT, Boespflut-Tanguy O, Day JW, Deconinck N, Klein A, Masson R, et al. FIREFISH Parts 1 and 2: 24-month safety and efficacy of risdiplam in infants with Type 1 SMA. Paper presented at the Muscular Dystrophy Association Clinical and Scientific Conference, Nashville, Tennessee, 13–16 March 2022.
10. Finkel RS, Farrar MA, Vlodavets D, Servais L, Zanoteli E, Al-Muhaizea M, et al. RAINBOWFISH: preliminary efficacy and safety data in risdiplam-treated infants with presymptomatic SMA (P17-5.003). Neurology. 2022;98(18 Suppl):1636.
11. Mercuri E, Baranello G, Boespflug-Tanguy O, De Waele L, Goemans N, Kirschner J, et al. Risdiplam in types 2 and 3 spinal muscular atrophy: a randomised, placebo-controlled, dose-finding trial followed by 24 months of treatment. Eur J Neurol. 2023;30(7):1945–56.
12. Mercuri E, Deconinck N, Mazzone ES, Nascimento A, Oskoui M, Saito K, et al. Safety and efficacy of once-daily risdiplam in type 2 and non-ambulant type 3 spinal muscular atrophy (SUNFISH part 2): a phase 3, double-blind, randomised, placebo-controlled trial. Lancet Neurol. 2022;21(1):42–52.
13. Zhu X. Comparison of nusinersen and Evrysdi in the treatment of spinal muscular atrophy. E3S Web Conf. 2021;271:03035.
14. Ribero VA, Daigl M, Martí Y, Gorni K, Evans R, Scott DA, et al. How does risdiplam compare with other treatments for types 1–3 spinal muscular atrophy: a systematic literature review and indirect treatment comparison. J Comp Eff Res. 2022;11(5):347–70.
15. Risdiplam (Evrysdi) for spinal muscular atrophy [internet]. Köln: Institute for Quality and Efficiency in Health Care; 2021 (https://www.gesundheitsinformation.de/risdiplam-evrysdi-bei-spinaler-muskelatrophie.html, accessed 6 October 2023).
16. Finkel RS, Dabbous O, Arjunji R, Droege M, Feltner DE, Novack A, et al. P.060 time to treatment effect in spinal muscular atrophy type 1 (SMA1): an indirect comparison of treatments. Can J Neurol Sci. 2019;46(S1):S30.
17. Canadian Agency for Drugs and Technologies in Health. CADTH reimbursement recommendation. Risdiplam (Evrysdi). Can J Health Technol. 2021;1(8):15.
18. Technical summary risdiplam (Evrysdi). HTA ID: 21006. Dublin: National Centre for Pharmacoeconomics; 2022 (https://ncpe.ie/wp-content/uploads/2022/03/Technical-summary-Risdiplam-HTAID-21006.pdf, accessed 6 October 2023).
19. Package advice risdiplam (Evrysdi®) for the treatment of 5q spinal muscular atrophy (SMA) [internet]. Diemen: National Health Care Institute (Zorginstituut Nederland); 2022 (https://english.zorginstituutnederland.nl/publications/reports/2022/07/15/package-advice-risdiplam-evrysdi, accessed 6 October 2023).
20. Risdiplam for treating spinal muscular atrophy [internet]. London: National Institute for Health and Care Excellence; 2021 (Technology appraisal guidance [TA755]) (https://www.nice.org.uk/guidance/ta755, accessed 6 October 2023).
21. Hu J, Sutherland CS, Aponte Ribero V, Zhu L, Hou X, Xia Y, et al. POSC94 cost-effectiveness of risdiplam versus nusinersen for treating patients with spinal muscular atrophy type 1 in China. Value Health. 2022;25(1):S105.
22. Dangouloff T, Vrščaj E, Servais L, Osredkar D. Newborn screening programs for spinal muscular atrophy worldwide: where we stand and where to go. Neuromuscul Disord. 2021;31(6):574–82.