Forslag om metodevurdering av vaksiner

Viktig informasjon – se på dette først!

- Innsendte forslag til en metodevurderinger på vaksiner vil bli publisert i sin helhet. Dersom forslagsstiller mener det er nødvendig informasjon for utfylling av skjemaet som ikke kan offentliggjøres ta kontakt før innsending. (e-post)

  Forslagsstiller er klar over at skjemaet vil bli publisert i sin helhet (kryss av): ☒

- Forslagsstiller har fylt ut punkt 16 nedenfor «Interesser og eventuelle interessekonflikter» (kryss av): ☒

- Dette skjema brukes for å sende inn forslag om metodevurdering på vaksiner. Skjema gjelder ikke forslag om forskningsprosjekter. En metodevurdering er en type kunnskapsoppsummering, og for at en slik skal kunne utføres behøves dokumentasjon eksempelvis fra gjennomførte kliniske studier. Manglende dokumentasjonsgrunnlag kan være en av årsakene til at det ikke gis oppdrag om en metodevurdering.

Kontaktinformasjon:

Navn på forslagsstiller (organisasjon/institusjon/foretak/produsent):

Sanofi-aventis Norge AS

Navn på kontaktperson:

Per Harald Aabakken

Telefonnummer:

+47 90982908

E-postadresse:

Per.aabakken@sanofi.com

Dato og sted:

16.03.2023, Lysaker, Norway

1. Forslagstillers tittel på forslaget:*
   *Denne kan endres under den videre behandlingen i systemet

Implementation of nirsevimab in the Norwegian childhood Immunization program for prevention of respiratory syncytial virus (RSV) lower respiratory tract disease in neonates and infants during their first RSV season.

2. Kort beskrivelse av vaksinen som foreslås vurdert:

Beyfortus received a marketing authorization valid throughout the EU on 31 October 2022.[1]

Summary points from SmPC:[2]

- Nirsevimab, active substance in Beyfortus, is an extended half-life human IgG1κ monoclonal antibody targeting the prefusion RSV F protein
- Beyfortus is indicated for the prevention of RSV lower respiratory tract infection (LRTI) in neonates and infants during their first RSV season
- The recommended dose of Beyfortus for infants entering their first RSV season is a single dose of 50mg IM for infants with body weight <5kg and a single dose of 100mg IM for infants with body weight ≥5kg
- Beyfortus provides protection for at least 5 months
- Beyfortus is formulated in a pre-filled syringe, available in two dosages (50mg/0.5mL and 100mg/1mL)

3. Kort beskrivelse av dagens tilbud (Hvilken metode (r), andre forebyggende tiltak, vaksiner brukes nå? Status for vaksinen (effekt, behandling, forlenget levetid etc.) Vil vaksinen som foreslås vurdert erstatte eller komme i tillegg til dagens tilbud?)

Current situation: There is currently no clinically effective antiviral treatment approved or recommended for RSV infection and no prophylactic option for *all* infants. The only current available option for RSV prophylaxis is palivizumab (Synagis). Palivizumab is restricted to high-risk infants including early preterm infants or infants < 2 years of age with congenital heart disease, immunodeficiency, or chronic lung disease (e.g., bronchopulmonary dysplasia and severe pulmonary hypertension). Palivizumab requires monthly administration during the RSV season. HELFO (The Norwegian Health Economics Administration) grants individual reimbursement for children meeting the criteria given by the Association of Pediatrics.[3,4]

Unmet need: There are currently no available RSV prophylaxis options for wider use in all infants, resulting in insufficient protection against RSV despite the substantial burden of RSV illness in otherwise healthy infants, both preterm and full term. Meaning there is an unmet need to protect all infants from RSV infection and illness.

Beyfortus was supported through European Medicines Agency's (EMA) PRIority MEdicines (PRIME) scheme in 2019, which provides early and enhanced scientific and regulatory support to promising new medicines that address unmet medical needs. Beyfortus was also evaluated under EMA's accelerated assessment mechanism because prevention of RSV infection in all infants is considered of major public health interest.[5]

Beyfortus received a marketing authorization valid throughout the EU on 31 October 2022.[1]

Beyfortus is indicated for the prevention of respiratory syncytial virus (RSV) lower respiratory tract disease in neonates and infants during their first RSV season. The recommended dose is a single dose of 50 mg administered intramuscularly for infants with body weight <5 kg and a single dose of 100 mg administered intramuscularly for infants with body weight ≥5 kg. Beyfortus should be administered prior to commencement of the RSV season, or from birth for infants born during the RSV season. Beyfortus is available in a 50 mg (50 mg/0.5 mL) and a 100 mg (100 mg/1 mL) pre-filled syringe.[2]

Nirsevimab, active substance in Beyfortus, is a recombinant neutralizing human IgG1κ long-acting monoclonal antibody (mAb) against the prefusion conformation of the RSV F protein. It has been modified with a triple amino acid substitution (YTE) in the Fc region to extend serum half-life. Nirsevimab binds with high affinity to a highly conserved epitope on the prefusion protein (antigenic site Ø). The dissociation constant (KD) is 0.12nM for RSV subtype A and 1.22nM for RSV subtype B. Nirsevimab inhibits the membrane fusion step in the viral entry process, neutralizing the virus and blocking cell-to-cell fusion. Based on clinical and pharmacokinetic data, nirsevimab has a duration of protection of at least 5 months.[2]

See section 11 for details regarding expected efficacy and safety of Beyfortus.

4. Hva gjelder forslaget?	Ja	Nei
En helt ny vaksine?	☒	☐
Et nytt bruksområde, eller en ny indikasjon for en etablert vaksine?	☒	☐
En sammenligning mellom flere vaksiner?	☐	☒

Er vaksinen tatt i bruk for denne indikasjonen?	☐	☒
Hvis ja – vaksinen tatt i bruk i vaksinasjonsprogram	☐	☒
Hvis ja, vaksiner har refusjon på §4	☐	☒

"Klikk her og skriv"

5. Hva omfatter forslaget - vaksinen (flere kryss mulig)?

Blå resept § 4	☐
Nasjonale vaksinasjonsprogram	☒
Beskriv	☒

Implementation of nirsevimab in the Norwegian childhood Immunization program for the prevention of RSV lower respiratory tract disease in neonates and infants during their first RSV season.

6. Vaksinens bruksområde:

I nasjonalt vaksinasjonsprogram	☒
Til smitteutsatte ved utbrudd i Norge	☐
Pre/Post-eksponering	☐
Allmennfarlig smittsom sykdom	☐
Annet	☐
Spesialisthelsetjenesten	☐
Primærhelsetjenesten	☐

"Klikk her og skriv"

7. Hvilke målgrupper gjelder vaksinen, og hvilke personer/pasienter berøres? (Får vaksinen evt. også konsekvenser for andre grupper (som personell, pårørende?)

Target group for immunization is neonates and infants for the prevention of RSV lower respiratory tract infection during their first RSV season.

8. Hvilke aspekter er relevante for vurderingen? (flere kryss mulig)

Klinisk effekt (virkninger på befolkningsnivå)	☒
Sikkerhet/bivirkninger	☒
Kostnader/ressursbruk	☒
Kostnadseffektivitet	☒
Organisatoriske konsekvenser	☒
Etiske	☒

Juridiske ☒

9. Foreslå hva som bør være hovedproblemstilling(er) for metodevurderingen av vaksinene, samt eventuelle underproblemstillinger (i samsvar med pkt. 8):

Assess the value of implementing nirsevimab in Norwegian childhood vaccination program and provide prevention against RSV lower respiratory tract disease in neonates and infants during their first RSV season.

10. Gi en kort begrunnelse for hvorfor det er viktig at metodevurderingen av vaksinen som foreslås bør gjennomføres:

Prevention of RSV infection in all infants is considered to be of major public health interest and an unmet need.[5] Beyfortus has been approved by EMA for the purpose of preventing serious lower respiratory tract disease caused by RSV in newborns and children during their first RSV season.[1]

See section 11 for more information about the burden of disease, and details regarding Beyfortus efficacy and safety data.

11. Kommenter vaksinen som forslås vurdert mht. følgende punkter:

Alvorlighetsgraden på tilstanden vaksinen er ment for

Respiratory syncytial virus (RSV) is a common contagious viral pathogen causing a wide spectrum of respiratory illness. Within the first year of life two-thirds of all infants are infected with RSV, and almost all children have been exposed by the age of two.[6]

RSV infections range from clinically insignificant to severe respiratory distress. RSV is a frequent cause of lower respiratory tract infections (LRTI) among infants and small children. Globally, an estimated 33.1 million RSV-associated LRTIs lead to 3.2 million hospital admissions and 59,600 in-hospital deaths each year in children < 5 years of age.[7]

Symptoms of RSV-LRTI include wheeze and cough and in severe cases tachypnoea, hypoxemia and cyanosis.[6] RSV is a leading cause of hospitalization in all infants, with RSV-LRTIs primarily manifesting as bronchiolitis and pneumonia. Most RSV hospitalizations occur in children < 12 months of age.[7] Infants with known risk factors, such as prematurity and underlying medical conditions, have an increased individual risk of severe RSV-LRTI, however most hospitalizations due to RSV occur in healthy infants born at term.[8,9,10]

Despite the high prevalence of the disease, few data are available on the RSV burden in Norway due to RSV not being included in the routine surveillance system. However, a hospital-based sentinel surveillance network (The Norwegian Enhanced Pediatric Immunization Surveillance) included RSV surveillance among children < 5 years of age during three consecutive winter seasons (2015-2018). Recent publication from the network demonstrated that of the children enrolled 40% were infected with RSV, and hospitalization incidence rate were 6 per 1000 children < 5 years in peak season 2016/2017[11]. The incidence or RSV was over 7 times higher amongst hospitalized infants under 12 months age (13.3/1000) than hospitalized infants aged 12-59 months (1.8/1000)[11]. Also, recent publications demonstrated that the **majority (85 %) of children < five years of age hospitalized with RSV are previously healthy and born at term**.[11,12] This means that the risk of severe RSV disease is unpredictable, and all infants are at risk of severe RSV infection.

Forventet effekt

Summary points on **safety** and **efficacy** from clinical trials:

Phase 1a (NCT02114268)[13] **and Phase1b/2a** (NCT02290340)[14]:

A favorable safety profile of nirsevimab in healthy adults (phase I) and healthy preterm infants (phase Ib/IIa), together with nirsevimab's extended half-life, support protection for the typical duration of a five-month RSV season after a single 50 mg intramuscular (IM) dose. Findings supported further clinical development of nirsevimab.

Phase 2b (NCT02878330)[15]:

Phase IIb trial for nirsevimab demonstrated robust efficacy in preventing medically attended RSV lower respiratory tract infection (LRTI; 70.1% relative risk reduction, p<0.001) and RSV LRTI hospitalization (78.4% relative risk reduction, p<0.001), with a safety profile comparable to placebo in healthy preterm infants (29-35 weeks gestational age [GA]) entering their first RSV season.

- The phase IIb trial also demonstrated that nirsevimab was associated with a low incidence of anti-drug antibodies, with no detected impact on the efficacy, safety, or pharmacokinetics of nirsevimab
- A pharmacokinetic analysis indicated that infants ≥5 kg had suboptimal exposure resulting in lower efficacy than infants <5 kg; the phase III and phase II/III trials were therefore adjusted to evaluate a higher dose level (100 mg) in infants ≥5 kg.

Phase 2/3 (Medley) (NCT03959488)[16]:

Phase II/III trial (Medley) is ongoing to assess the safety, pharmacokinetics, anti-drug antibody response and descriptive efficacy of nirsevimab relative to palivizumab in palivizumab eligible preterm infants (≤35 weeks GA) and infants with chronic lung disease (CLD)/congenital heart disease (CHD) entering their first or second RSV seasons (estimated to be completed in March 2023).

- At the primary analysis, nirsevimab had a similar safety profile to palivizumab among preterm infants and infants with CHD/CLD during their first RSV season
- Serum levels of nirsevimab were comparable between the preterm and CHD/CLD cohorts
- Anti-drug antibody responses were low and comparable between the nirsevimab and palivizumab treatment arms
- The incidence of medically attended RSV LRTIs was low and comparable among infants receiving nirsevimab and palivizumab

Phase 3 (Melody) (NCT03979313)[17]:

Phase III trial (Melody) is ongoing to assess the efficacy, safety, pharmacokinetics, and anti-drug antibody response of nirsevimab relative to placebo in healthy late preterm and term infants (≥35-week GA; estimated to be completed in August 2023) entering their first RSV season.

- At the primary analysis, nirsevimab was associated with a 74.5% relative reduction in medically attended RSV LRTI (p<0.001) and a 62.1% relative reduction in hospitalizations for RSV LRTI (p=0.07)
- Nirsevimab had a similar safety profile to placebo, with similar rates of AEs and SAEs in both groups
- The incidence of ADAs was low; when ADAs were detected, there was no observed effect on nirsevimab pharmacokinetics through Day 151 or safety

Pre-specified pooled analysis of Phase 2b + Phase 3 (Melody)[18]:

A pre-specified pooled analysis of data from the phase IIb trial and phase 3 (Melody) was conducted to obtain a single point estimate of efficacy in all infants (term and preterm).

- This pre-specified pooled analysis of the phase IIb (<5 kg receiving 50mg) and phase III primary efficacy cohorts showed consistent efficacy against MALRTI of different severities **(79.5% against MALRTI [p<0.0001]; 77.3% against MALRTI with hospitalization [p=0.0002]; 86.0% against very severe MALRTI [p<0.0001]).**
- Beyond the direct benefit in disease prevention, there was an associated benefit through the reduction in health-resource use and prescribed antibiotics for any indication.
- In addition, based on similar pharmacokinetic data, a similar level of efficacy to that found in the pooled analysis is extrapolated to infants with chronic lung disease or congenital heart disease and those with born extremely preterm at less than 29 weeks gestational age.

Sikkerhet (beskriv kort opplysninger om kjente risikoforhold, sikkerhetsaspekter og bivirkninger)

Se previous section for summary points of clinical trials on efficacy and safety.

Safety profile summary points:[2]

Contraindications: Hypersensitivity to the active substances or to any of the excipients (L-histidine, L-histidine hydrochloride, L-arginine hydrochloride, sucrose, polysorbate 80 or water for injections)

Special warning and precautions for use:
Traceability: To improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded).
Hypersensitivity including anaphylaxis: Serious hypersensitivity reactions, including anaphylaxis, have been observed with monoclonal antibodies. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration, and initiate appropriate medicinal products and/or supportive therapy.
Clinically significant bleeding disorders: As with any other intramuscular injections, nirsevimab should be given with caution to infants with thrombocytopenia or any coagulation disorder.

Undesirable effects: The most frequent adverse reaction was rash (0.7%) occurring within 14 days post dose. The majority of cases were mild to moderate in intensity. Additionally, pyrexia and injection site reactions were reported at a rate of 0.6% and 0.4% within 7 days post dose, respectively. Injection site reactions were non-serious.

Table 1 presents the adverse reactions reported in 1 955 term and preterm infants (GA ≥29 weeks) who received nirsevimab in clinical trials.

Table 1: Adverse reactions

MedDRA SOC	MedDRA Preferred Term	Frequency
Skin and subcutaneous tissue disorders	Rash[a]	Uncommon
General disorders and administration site conditions	Injection site reaction[b]	Uncommon
	Pyrexia	Uncommon

[a] Rash was defined by the following grouped preferred terms: rash, rash maculo-papular, rash macular.
[b] Injection site reaction was defined by the following grouped preferred terms: injection site reaction, injection site pain, injection site induration, injection site oedema, injection site swelling.

Totalt antall pasienter i Norge vaksinen er aktuell for

Full birth cohort (55 000 children) < 1 year old their first RSV season

Konsekvenser for ressursbruk i helsetjenesten

RSV infections in infants and young children are associated with a substantial economic burden, both because of considerable healthcare resource utilization and direct medical costs, as well as indirect costs arising from reduced productivity in parents of children with RSV. RSV-related direct medical costs globally (including hospital, outpatient, and follow-up care) were estimated at €4.82 billion in 2017.[19]

Few studies have assessed the indirect costs associated with RSV infections in infants and young children. According to four studies conducted in the US and Spain, RSV infections in children are associated with indirect monetary costs as well as lost productivity of their parents and caregivers.[20-23]

RSV infections result in impaired health-related quality of life (HRQoL) in infants and their caregivers, as well as nosocomial infections and antibiotic misuse which affect the wider public.[24-29]

Behov for revisjon av eksisterende nasjonale faglige retningslinjer, evt. utarbeidelse av nye

Current guidelines for prevention of RSV with palivizumab (Synagis) is restricted to high-risk infants (early preterm infants or infants < 2 years of age with congenital heart disease, immunodeficiency, or chronic lung disease (e.g., bronchopulmonary dysplasia, severe pulmonary hypertension). Palivizumab also requires monthly administration during the RSV season.[3] Implementation of nirsevimab in the Norwegian childhood vaccination program will trigger the need for revision of the current guidelines to make RSV prophylaxis available for all children.

12. Oppgi referanser til dokumentasjon om vaksinens effekt og sikkerhet (eks. tidligere metodevurderinger). (Inntil 10 sentrale referanser oppgis. Ikke send vedlegg på dette trinnet i prosessen.)

Nirsevimab efficacy and safety was assessed in the following clinical trials and publications:

Phase 1a (NCT02114268): Griffin MP et al. Safety, Tolerability, and Pharmacokinetics of MEDI8897, the Respiratory Syncytial Virus Prefusion F-Targeting Monoclonal Antibody with an Extended Half-Life, in Healthy Adults. *Antimicrob Agents Chemother.* 2017;23(3):e0714-16. https://doi.org/10.1128/aac.01714-16

Phase1b/2a (NCT02290340): Domachowske JB et al. Safety, Tolerability and Pharmacokinetics of MEDI8897, an Extended Half-life Single-dose Respiratory Syncytial Virus Prefusion F-targeting Monoclonal Antibody Administered as a Single Dose to Healthy Preterm Infants. *Pediatr Infect Dis J*. 2018;37(9):886-892. https://doi.org/10.1097/inf.0000000000001916

Phase 2b (NCT02878330): Griffin MP et al. Single-Dose Nirsevimab for Prevention of RSV in Preterm Infants. *N Engl J Med*. 2020;383(5):415-425. Erratum in: *N Engl J Med*. 2020;383(7):698. https://doi.org/10.1056/nejmoa1913556

Phase 2/3 (Medley) (NCT03959488): Domachowske JB et al. Safety of Nirsevimab for RSV in Infants with Heart or Lung Disease or Prematurity. *N Engl J Med*. 2022;386:892-894. https://doi.org/10.1056/nejmc2112186

Phase 3 (Melody) (NCT03979313): Hammitt LL et al. Nirsevimab for Prevention of RSV in Healthy Late-Preterm and Term Infants. *N Engl J Med*. 2022;386:837-46. https://doi.org/10.1056/nejmoa2110275

Pre-specified pooled analysis phase2b + phase3 (Melody): Simões EAF et al. Efficacy of nirsevimab against respiratory syncytial virus lower respiratory tract infections in preterm and term infants, and pharmacokinetic extrapolation to infants with congenital heart disease and chronic lung disease: a pooled analysis of randomised controlled trials. *Lancet Child Adolesc Health*. 2023 Jan 9;S2352-4642(22)00321-2. https://doi.org/10.1016/S2352-4642(22)00321-2

13. Oppgi navn på produsenter/leverandører vedrørende vaksinen (dersom aktuelt/tilgjengelig):

Sanofi-aventis Norge AS

14. Status for markedsføringstillatelse (MT): (Når forventes MT? Eventuelt opplysning om planlagt tidspunkt for markedsføring).

Beyfortus received a marketing authorization valid throughout the EU on 31 October 2022.[1]

Astra Zeneca AB is marketing authorization holder. Sanofi-aventis Norge AS is local representative and is responsible for the commercialization of nirsevimab in Norway.

15. Fritekstrubrikk (Supplerende relevant informasjon, inntil 300 ord.)

16. Interesser og eventuelle interessekonflikter

Beskriv forslagstillers relasjoner eller aktiviteter som kan påvirke, påvirkes av eller oppfattes av andre å ha betydning for den videre håndteringen av vaksinen som foreslås metodevurdert. (Eksempler: Forslagsstiller har økonomiske interesser i saken. Forslagsstiller har eller har hatt oppdrag i tilslutning til eller andre bindinger knyttet til vaksinen eller aktører som har interesser i vaksinen.)

Marketing authorization holder: Astra Zeneca AB Local representative: Sanofi-aventis Norge AS

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