EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Mr Sandro Venturini,
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28 July 2025

EMA/244652/2025

Sent by email only:
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Dear Mr Sandro Venturini,

Subject: International Legal Complaint for Crimes Against Humanity and Unauthorised Medical Experimentation on Newborns.

With this letter the European Medicines Agency (EMA) is following up to the "*Official international denunciation document*" (Denunciation Document) received on 12 May 2025, where you state that the approval of Beyfortus ® (active substance: Nirsevimab), a medicinal product authorised in 2022 pursuant to Article 8(3) of Regulation (EC) No 736/2004, and the clinical trials carried out during its development represent*, inter alia*, a crime against humanity.

More specifically, you claim that:

> "*The systematic inoculation of an experimental biological drug in healthy newborns, with incomplete data and flawed consent, may constitute a violation of Art. 7* (of the Rome Statute)*, in conjunction with the provisions on the inviolability of the human body and the protection of childhood*".

In the Denunciation Document, you also request EMA:

> **a.** to carry out an urgent review of the authorisation process of Beyfortus ® for use in paediatrics.
>
> **b.** to proceed with the precautionary suspension of the marketing authorisation (MA) of Beyfortus with immediate effect, pursuant to Article 23 of Regulation (EC) No 726/2004.

To support these requests, you shared the results of a "*structural analysis of Nirsevimab, conducted with cryo-electron microscopy*" which allegedly highlighted certain critical elements, such as neonatal toxicology (FcRn receptor saturation, liver damage, indirect immune effects) and included data referring to 1) the critical molecular profile, 2) Advanced Neonatal Toxicology, 3) Risk predictive models, without however further explaining the relevance of such data.

On the basis of the above, you consider EMA responsible for not having taken into account Long-Term immunogenicity data:

"*EMA guideline on the immunogenicity of biological medicines (EMA/CHMP/BMWP/14327/2006 Rev.1) states that immunogenicity should be thoroughly assessed, especially for medicines intended for vulnerable populations such as neonates. In the case of nirsevimab, its prolonged half-life (about 28.9 days in neonates) implies a significant persistence in the body, increasing the risk of development of anti-drug antibodies (ADA).* ***The absence of a comprehensive long-term immunogenicity assessment could represent a negligence in the application of the safety standards required for the marketing of biological medicines intended for such a sensitive paediatric population***".

In addition, you state that the request for an urgent review of the authorisation process of Beyfortus is also supported by:

"*Some international reports (eg ANSM France, April 2024)* which *indicate an increase in neonatal mortality and thrombotic adverse events*".

* * *

Bearing the above in mind, we would like to provide some clarifications on the main points addressed to EMA by the Denunciation Document as follows.

1. Regarding the claim that EMA is responsible for not having taken into account Long-Term immunogenicity data during the assessment of the initial marketing authorisation for Beytrofus.

As a preliminary remark, it is worth recalling that the European Commission has issued a marketing authorisation for Beyfortus for the following therapeutic indication as noted in the EU Product Information (PI):

Beyfortus is indicated for the prevention of Respiratory Syncytial Virus (RSV) lower respiratory tract disease in:
i. Neonates and infants during their first RSV season.
ii. Children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season (see section 5.1).

For 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 from birth for infants born during the RSV season. For others born outside the season Beyfortus should be administered ideally prior to the RSV season.

For children who remain vulnerable to severe RSV disease through their second RSV season, the recommended dose is a single dose of 200 mg given as two intramuscular injections (2 x 100 mg). Beyfortus should be administered ideally prior to the start of the second RSV season.

For further details on posology, see section 4.2 of the Beyfortus EU Summary of Product Characteristics (SmPC) (Beyfortus: EPAR – Product information).

Information on the development of anti-drug antibodies (ADA) and long-term safety in the Beyfortus SmPC and Beyfortus Risk Management Plan (RMP) are respectively displayed as follows:

- Immunogenicity (EU SmPC, Section 5.1):
  Anti-drug antibodies (ADA) were commonly detected.
  The employed immunogenicity assay has limitations in detecting ADAs at early onset (prior to Day 361) in the presence of high concentrations of drug, therefore, the incidence of ADA might not have been conclusively determined. The impact on clearance of nirsevimab is uncertain. Subjects who were ADA positive at Day 361 had reduced nirsevimab concentrations at Day 361 compared to subjects who received nirsevimab and were ADA-negative.
  The impact of ADA on the efficacy of nirsevimab has not been determined. No evidence of ADA impact on safety was observed.

- Potential Risks also not Considered Important (RMP, Section 2.7.1.1)
  Immune complex disease (Type III hypersensitivity):

Nirsevimab, like other biologics, can induce the development of ADA and the occurrence of such ADA could result in immune complex disease or altered nirsevimab levels or activity. Drug-induced immune complex (type III) hypersensitivity reactions can occur when the host immune system generates antibodies to drug resulting in soluble circulating antigen-antibody complex formation and their deposition in blood vessels. Immune complex disease can manifest in the form of a number of conditions such as vasculitis, endocarditis, neuritis, glomerulonephritis, serum sickness, and arthralgias. There were a limited number of subjects (n = 110; 5.9%) in the pivotal studies who were ADA positive post baseline. Although the numbers were small and data were limited, ADA did not appear to impact the safety or overall efficacy of nirsevimab. In addition, there have been no events of immune complex disease reported in the nirsevimab clinical development programme. This risk is not considered to alter the risk-benefit profile of nirsevimab. Therefore, the risk of immune complex disease is considered to be a potential risk not categorised as important for inclusion in the RMP.

- New Safety Concerns and Reclassification With a Submission of an Updated RMP (RMP, Section 2.7.2)
  Long-term safety previously classified as missing information is removed from the list of safety concerns. During review of the marketing authorisation application (EMEA/H/C/005304/0000), long-term safety was added as "missing information" and MELODY (D5290C00004) and MEDLEY (D5290C00005) were included as additional pharmacovigilance activities. Final long-term safety data from these studies are consistent with data up to Day 360, with no change to the favourable safety profile described in the previous submissions. Safety results from the second RSV season (Day 362 to 511) in MELODY did not show any increase in the cases of MA RSV LRTI and no increased severity of disease for infants administered nirsevimab compared with infants administered placebo.

With reference to the claim related to the purported lack of consideration by EMA of long-term immunogenicity data especially with respect to the development of anti-drug antibodies (ADA) during the assessment of Beyfortus, it is important to clarify that the assessment of immunogenicity data refers to primarily the safety aspects of the medicinal product under discussion.

As noted in the EMA Guideline on Immunogenicity assessment of therapeutic proteins (EMEA/CHMP/BMWP/14327/2006 Rev 1, 18 May 2017) therapeutic proteins are recognized by the human immune system. This recognition is often followed by an immune response to therapeutic proteins. This potentially harmful immune response is complex and, in addition to ADA formation, involves T cell activation and innate immune responses. The consequences of an immune reaction to a therapeutic protein range from transient appearance of ADAs without any clinical significance to severe life-threatening conditions. Potential clinical consequences of an unwanted immune response include loss of efficacy of the therapeutic protein, serious acute immune effects such as anaphylaxis, and, for therapeutic proteins used for substitution, cross-reactivity with the endogenous counterpart.

In regard to the safety aspects, it should be stressed that when submitting a marketing authorisation application (MAA) pursuant to Article 8(3) of Regulation (EC) No 726/2004, as it is the case for Beyfortus, applicants are required to submit a RMP to EMA. RMPs are assessed by EMA during initial marketing authorisation procedures and are published after the adoption of the Commission decision granting the marketing authorisation (MA). RMPs are constantly modified and updated throughout the lifetime of a medicinal product as new information becomes available. In the case of Beyfortus, a RMP was evaluated during the assessment of the initial MAA which concluded with the issuing of a MA on 31 October 2022. Further updates were made to the RMP following two type II variations as noted in the EMA website for Beyfortus (Beyfortus | European Medicines Agency (EMA)).

From the RMP for Beyfortus, it results that the identified risk window for Respiratory syncytial virus (RSV) disease is primarily in the first year of life. As stated, *"In European countries, the hospitalisation rates were highest for infants within the first year of life, 19 to 22 per 1000 children"* (Jansen et al. 2007; Van Gageldonk-Lafeber et al. 2005; Weigl et al. 2001). This risk extends into the second RSV season, with an RSV-attributable hospitalisation rate for respiratory disease of approximately 2.5 per 1000 population estimated in children aged 6 to 23 months in the UK between 1995 and 2009 (Taylor et al 2016). Therefore, the current indication and posology for Beyfortus cover the period of highest risk RSV disease in the paediatric population.

Furthermore, as referred in section 2.6.8.7 of the Assessment Report for Beyfortus, INN-nirsevimab, the overall safety profile by age is discussed as follows:

- In the MELODY/Study 3 (All) Safety Pool, 358 subjects received nirsevimab, out of 533 neonates (<28 days at randomisation) included in the subgroup analyses. All neonates received the proposed dose. The distribution of adverse events (AEs) was generally comparable between treatment groups, though a slightly higher proportion of subjects in the nirsevimab group reported at least one serious AE (14.5% vs. 12.0%) and at least one serious and/or ≥ Grade 3 event (15.1% vs. 12.6%). Additionally, there was a higher percentage of subjects in the nirsevimab group reporting at least one AESI based on investigators assessment (0.6% (n=2) vs. 0%). For age of randomisation (≤ 3.0 Months, > 3.0 to ≤ 6.0 Months, and> 6.0 Months) there were no apparent discrepancies with regards to distribution of AEs.
- In the MEDLEY study, the distribution of AEs was generally balanced between the treatment arms for the subgroups of ages ≤ 3-months and > 3.0 to ≤ 6.0 Months. However, there was a higher percentage AEs in subjects in the > 6-month age subgroup in the nirsevimab treatment arm (68.7% (46/103) vs. 58.3 (21/36). There was also a higher percentage of ≥1 serious or ≥Grade 3 event (9.0% (6/67) vs. 2.8% (1/36) and 7.5% (5/67) in the nirsevimab group that had ≥ AESI based on selected MedDRA codes. There were 9.0% (6/67) vs. 0% that had ≥ 1 event related to COVID-19.

Besides the overall conclusion on this aspect in section 3.7.1 of the abovementioned EPAR, the observations are considered to be due to reactogenicity (capacity of nirsevimab to produce common, "expected" adverse reactions), with no expectation of more serious adverse events:

> Regarding the effect of age in the MEDLEY study there is a trend for more adverse events in neonates > 6-months in the nirsevimab treatment arm. Also, there were more subjects in the nirsevimab group that had ≥ 1 AE related to COVID-19. As the latency of onset of COVID-19 related events in MELODY and MEDLEY was well after dosing of nirsevimab with the earliest onset in the nirsevimab group on Day 218 and Day 66, respectively, no interference of nirsevimab administration with COVID-19 infection was reported. A review of cases suggestive of reactogenicity did not suggest any anticipation of more serious adverse events in infants> 6-month even though infants> 6-month age subgroup has a more developed immune system and thus potential for reactogenicity.

In the assessment of infants and children up to 24 months of age supporting the extension of the indication up to 24 months of age (Beyfortus II-05 - EPAR AR), no new adverse drug reactions were identified in the MEDLEY Study (preterm infants and infants and children up to 24 months of age with CHD or CLD, compared to palivizumab) or in the open-label MUSIC Study (in immunocompromised infants up to 24 months of age). With regards to safety in special populations, in the MEDLEY Study, 6 subjects weighed < 7 kg on Season 2 Day 1, hereof 4 in the NIRS/NIRS group. These 4 subjects reported 23 TEAEs in total, predominantly in the SOC's of infections and infestations and (4 subjects) Gastrointestinal disorders (4 subjects). Three of the subjects experienced Grade 3 TEAEs. None of the TEAEs were considered IP-related. None were AESIs, a d none were ADA positive post baseline. It is acknowledged that no exposure-dependent safety relationship for nirsevimab would be anticipated given the MOA, and no clear causality between events and IP can be concluded upon.

It shall be also noted that the potential for anti-drug antibodies (ADAs) was investigated in non-clinical and clinical studies:

- The translational value of ADA formation in animal models is limited. Nevertheless, formation of ADA was assessed based on data from the 1-month repeat-dose study in cynomolgus monkeys with a 25-week recovery period. None of the animals in the control or treated groups tested positive for ADA at any time point during the treatment phase. ADAs to nirsevimab was only observed in the recovery period and in a limited number of animals (four (22.2%) of the recovery animals). Although it is unclear what effect ADAs had on the Toxicokinetics (TK), sufficient exposures appear to have been achieved.
- Clinically, referring to the section 2.6.2.3 of the EPAR, ADA results were generally consistent across subgroups (term/preterm, weight, CHD/CLD). On Day 361, serum nirsevimab concentrations were generally lower in participants with ADA, including a larger proportion being below the limit of quantification, compared with those who tested negative; this indicates an influence of ADA on nirsevimab PK between Days 151 and 361.
- Lastly, as per section 2.6.3, ELISA-based assays were developed and validated for determination of nirsevimab serum concentrations, detection of ADAs to nirsevimab (screening/confirmation), NAbs to nirsevimab and ADAs to the M257Y/S259T/T261E triple amino acid substitution (YTE) of nirsevimab. As noted in the SmPC ("immunogenicity assay has limitations in detecting ADAs at early onset (prior to Day 361))" the quantification assay was not tolerant for ADAs at ADA concentrations >100 ng/mL. The drug tolerance of the ADA assay

was 12.5 µg/mL for detection of 100 ng/mL ADA against nirsevimab, which allows detection of sustained ADA positivity after Day 151. As exposure until day 151 was not obviously affected in the large majority of ADA positive subjects, findings do not raise a certain concern. In addition, the safety assessment confirmed that there were no safety issues linked to ADA presence.

Regarding immunogenicity as a safety concern, it is considered minor, particularly if the product is intended for single-use administration. ADA incidence was low and had no observable effect on PK prior to Day 151 of post-administration. Beyond day 151 there is an indication of changed PK due to ADA as serum concentrations of nirsevimab were lower in ADA positive subjects at day 361. In the target population, the impact of ADAs on exposure seems to be mainly present in the elimination phase post day 151 and might presumably be attributed to ADAs against YTE substitution.

Regarding immunogenicity in infants and children up to 24 months of age (Beyfortus II-05 - EPAR AR), in MEDLEY RSV Season 2, all-over, post-baseline ADA against nirsevimab in RSV Season 2 was found in one subject (2.5% n=1/40). Importantly, there was no registration of nirsevimab related AEs, AESIs, or skin hypersensitivity through 360 days post nirsevimab administration. In the MUSIC Study, interim CSR, a total of 4.1% of subjects (n=4/97) with available ADA-samples were positive, and had no registration of IP-related AEs, AESIs, or skin hypersensitivity. In the final CSR of the MUSIC study the ADA incidence was 11.3% (11/97 subjects). A total of two subjects, ADA-positive on day 361, experienced TEAEs, of which one was a nirsevimab-related TEAE of Grade 1 pyrexia occurring within 60 minutes of IP administration, and the other was a Grade 1 skin reaction (macular rash) on Day 361 considered non-related to nirsevimab.

The Applicant submitted final bioanalytical reports covering MELODY and MEDLEY accordingly. ADAs were commonly observed with nirsevimab, though early detection was limited, and their impact on the drug's clearance and efficacy remains unclear; however, there were no safety issues linked to ADA presence. Although ADAs could theoretically lead to immune complex disease, no such events occurred during clinical trials, and the limited data showed no effect on safety or efficacy, so this potential risk is not considered important in the Risk Management Plan.

Finally, the section 2.6.4 concludes that ADA incidence was overall low across the clinical trial programme:

The efficacy in the context of ADA presence was also evaluated (cf. section 2.6.5.6 of the EPAR):

- There was a tendency of a higher incidence of MA RSV LRTI +/- hospitalisation in subjects with ADA compared with subjects without ADA in MELODY (Table 23). As such 13.3% of subjects with ADA had an event whereas only 1.0% of subjects without ADA had an event. For hospitalisation, the incidence was 6.7% vs 0.5% for ADA positive and ADA negative subjects, respectively.
  This tendency was although not so clear in Study 3, where 3.8% of ADA positive had an event and 2.5% of ADA negative had an event. For hospitalisation, the opposite was seen 0% vs 0.8%.

Safety with respect to ADA is also discussed (cf. section 2.6.8.8 - Immunogenicity and Safety):

- Overall, the percentages of subjects that were ADA-positive in the 3 pivotal safety studies were low (ADA positivity was defined as a titre of ≥ 50 for nirsevimab). In the MELODY/Study 3 (All) Safety Pool, 5.9% (110/1880) of subjects in the nirsevimab group and 2.3% (22/942) of subjects in the placebo group were ADA positive to nirsevimab post baseline through day 361. In the MEDLEY study, numbers were small: 2.1% (12/581) subjects in the nirsevimab group and 5.2% (15/286) in the palivizumab group were ADA-positive (90% of subjects had samples available for ADA assessment at Day 151 and 38% of subjects had available samples at Day 361).
  Overall, no safety concerns related to ADA were raised from safety data from the MELODY/Study 3 (All) Safety Pool or MEDLEY study (including the preterm and CLH/CHD cohorts). No related immunogenicity (IP-related AE, investigator-assessed skin hypersensitivity reaction, or AESI) was observed in ADA-positive subjects, including no immune complex diseases.

The sections 2.6.8 and 2.6.9 of the EPAR support the above conclusions, highlighting that ADA rates were low and no safety concerns or immune reactions were associated with ADA positivity:

- Overall, the percentages of subjects that were ADA-positive in the 3 pivotal safety studies were low and no safety concerns related to ADA were raised and no related immunogenicity (IP-related AE, investigator-assessed skin hypersensitivity reaction, or AESI) was observed in ADA-positive subjects, including no immune complex diseases.

In addition the evaluation of immunogenicity in infants and children up to 24 months of age (Beyfortus II-05 - EPAR AR) raises no apparent safety concerns after administration of a second dose of nirsevimab.

Finally, the sections 5.1 and 2.7.1.1 of the Beyfotus EU Product Information (PI) and Beyfortus RMP , are respectively displayed as follows:

- Anti-drug antibodies (ADA) were commonly detected.
  The employed immunogenicity assay has limitations in detecting ADAs at early onset (prior to Day 361) in the presence of high concentrations of drug, therefore, the incidence of ADA might not have been conclusively determined. The impact on clearance of nirsevimab is uncertain. Subjects who were ADA positive at Day 361 had reduced nirsevimab concentrations at Day 361 compared to subjects who received nirsevimab and were ADA-negative.
  The impact of ADA on the efficacy of nirsevimab has not been determined. No evidence of ADA impact on safety was observed.

- Potential Risks also not Considered Important
  Immune complex disease (Type III hypersensitivity):
  Nirsevimab, like other biologics, can induce the development of ADA and the occurrence of such ADA could result in immune complex disease or altered nirsevimab levels or activity. Drug-induced immune complex (type III) hypersensitivity reactions can occur when the host immune system generates antibodies to drug resulting in soluble circulating antigen-antibody complex formation and their deposition in blood vessels. Immune complex disease can manifest in the form of a number of conditions such as vasculitis, endocarditis, neuritis, glomerulonephritis, serum sickness, and arthralgias. There were a limited number of subjects (n = 110; 5.9%) in the pivotal studies who were ADA positive post baseline. Although the numbers were small and data were limited, ADA did not appear to impact the safety or overall efficacy of nirsevimab. In addition, there have been no events of immune complex disease reported in the nirsevimab clinical development programme. This risk is not considered to alter the risk-benefit profile of nirsevimab. Therefore, the risk of immune complex disease is considered to be a potential risk not categorised as important for inclusion in the RMP.

In summary, the incidence of ADAs was low and did not raise safety concerns across the pivotal studies. The evidence presented in the final bioanalytical reports showed no effect on safety or efficacy, and it was concluded that this potential risk is not considered important in the Risk Management Plan.

The existing data suggests that following the administration of the recommended single dose of the product, the impact of ADA on both safety and efficacy is likely negligeable.

2. Regarding the results of a "*structural analysis of Nirsevimab, conducted with cryo-electron microscopy*".

As mentioned above, the Denunciation Document includes the results of a "*structural analysis of Nirsevimab, conducted with cryo-electron microscopy*" which allegedly highlighted certain critical elements, such as neonatal toxicology (FcRn receptor saturation, liver damage, indirect immune effects) and included data referring to 1) the critical molecular profile, 2) Advanced Neonatal Toxicology, 3) Risk predictive models.

However, since no explanation regarding the relevance of such data has been provided, the Agency cannot provide any immediate comment. Nevertheless, the Agency would like to provide the following clarifications regarding the assessment of the quality of Beyfortus carried out by the Commitee for Human Medicinal Products (CHMP).

Nirsevimab is an IgG1 monoclonal antibody, a well-established and well-characterised class of active substances. In the context of the marketing authorisation application (MAA) for Beyfortus, nirsevimab was characterised using state-of-the-art analytical methods to determine elements including:
- Its structure (primary, secondary, tertiary, post-translational modifications);
- Its glycosylation profile;
- Its biological activity including Fc effector functions;
- Its product-related substances/impurities and process-related impurities;
- Its degradation pathways.

The active substance and finished product are controlled for their key characteristics before release of every batch on the EU market, in line with the approved specifications. Specifications to cover the shelf life of the active substance and finished product are also in place. As a general principle, marketing authorisation holders (MAHs) for centrally authorised medicinal products have the obligation to report promptly to EMA out-of-specification results. Information on this matter is available on EMA website: www.ema.europa.eu/en/human-regulatory-overview/post-authorisation/compliance-post-authorisation/quality-defects-recalls.

As indicated in the Beyfortus product information, the active substance is formulated with polysorbate 80, a commonly used excipient for monoclonal antibodies to reduce protein aggregation. As for all medicinal products, CHMP reviewed the adequacy of the Beyfortus formulation and pharmaceutical development.

At the time of adopting an Opinion for the MAA (on 15 September 2022), CHMP considered that the overall quality of Beyfortus is acceptable when used in accordance with the conditions defined in the product information. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing CHMP and ICH guidelines.

3. Regarding *some international reports (eg ANSM France, April 2024)* which *indicate an increase in neonatal mortality and thrombotic adverse events.*

EMA continues to rigorously monitor the safety of all medicines and vaccines authorised for use in the EU including nirsevimab. Currently, there are no signal procedures ongoing for this product. As defined by the legislation, signal is information arising from one or multiple sources which suggests a new potentially causal association, or a new aspect of a known association between an intervention and an event, that is judged to be of sufficient likelihood to justify verificatory action. More on signal management process can be found here: Guideline on good pharmacovigilance practices (GVP) - Module IX – Signal management (Rev 1).

All the suspected adverse drug reactions are reported in the European (available at the following link: https://www.adrreports.eu/index.html).

For completeness, the company submitted results of the MELODY (primary cohort) and the MEDLEY clinical trials as part of its MAA for Beyfortus. EMA's CHMP extensively reviewed the results of these trials and concluded that the benefit risk balance of the use of Beyfortus in babies is clearly positive. More details on the CHMP's evaluation are available in the public assessment report.

The company subsequently submitted further results of the MELODY trial (Safety Cohort) as part of a post-authorisation variation procedure. The CHMP thoroughly reviewed these data and concluded that the benefit-risk balance of Beyfortus remained positive and the product information was updated to reflect the additional safety and efficacy data. Notably, thrombosis is not listed as an adverse reaction. Only adverse reactions with at least a reasonable possibility of a causal relationship to the medicinal product—based on clinical trials, post-authorisation studies, or spontaneous reports—are included in the product information. Events for which no such relationship is suspected are not listed.

The company has also submitted safety data from the ongoing HARMONIE trial as part of its periodic safety update reports (PSURs). These data were reviewed by the EMA and assessed during the June 2025 CHMP plenary session, in the context of the 4th PSUSA (PSUSA/00011026/202410, covering the period from 1 May 2025 to 30 October 2025). Based on this assessment, no changes to the product information were deemed necessary. The MAH presented relevant efficacy and effectiveness results from the first-year analysis of the HARMONIE study, as well as from published real-world studies, all of which confirmed the existing efficacy profile of nirsevimab. No new efficacy data emerged that would alter previous assessments. The MAH also reported no significant safety concerns in the long-term follow-up from the HARMONIE study extension.

Accordingly, the CHMP concluded at its June 2025 plenary meeting that the benefit-risk balance of medicinal products containing nirsevimab remains unchanged, and it recommended the continued maintenance of the marketing authorisation. In light of these findings, the frequency of PSUR submission was revised from every six months to annually, with the updated Union Reference Dates (EURD) list reflecting this change (publication dated 25 June). The Pharmacovigilance Risk Assessment Committee (PRAC) has also agreed on 5 June 2025 that future data lock points (DLPs) for PSURs should fall after the RSV epidemic season—specifically in the spring—rather than before. Since Beyfortus is primarily used in winter, and use is minimal during the summer months between epidemics, the next PSUR DLP is confirmed as 30 April 2025, in line with the current EURD list. https://www.ema.europa.eu/en/documents/other/list-european-union-reference-dates-eurd-frequency-submission-periodic-safety-update-reports-psurs_en.xlsx

In evaluating reports of suspected side effects—including those with fatal outcomes—the EMA and national competent authorities look for unusual or unexpected patterns in the data, such as an event occurring more frequently among treated patients than in the general population. These findings are assessed in conjunction with data from clinical trials, observational studies, and scientific literature. If a safety concern is identified and there is at least a reasonable possibility that the medicine caused the event, regulatory authorities take appropriate measures. These may include updating the product information with new side effects, warnings, or contraindications; issuing public communications; or, in rare cases, suspending the use of the medicine.

Finally, it is important to highlight that the World Health Organization (WHO) recognises that the greatest burden of RSV disease occurs in otherwise healthy, full-term infants. As such, WHO recommends universal protection—either through maternal vaccination (providing transplacental IgG) or through the use of long-acting monoclonal antibodies. As reported in the "Highlights from the Meeting of the Strategic Advisory Group of Experts (SAGE) on Immunization 23-26 September 2024", https://cdn.who.int/media/docs/default-source/immunization/sage/2024/september/sage-sept_2024-highlights_final.pdf?sfvrsn=6a0f811d_3 the WHO's Strategic Advisory Group of Experts (SAGE) endorsed passive immunisation for the prevention of severe RSV disease in infants, supporting the use of both long-acting monoclonal antibodies and maternal immunisation strategies.

4. Regarding the request to carry out an urgent review of the authorisation process of Beyfortus ® for use in paediatrics.

Given the responses provided under sections 1 and 3 of this letter, at present there is no evidence to justify a review of the authorisation process of Beyfortus for use in paediatrics.
In particular, under section 1, it is demonstrated that both the long-term safety and immunogenicity data were taken into consideration at the time of the MAA.
Moreover, as reported in section 3, through the periodic safety update reports (PSURs) it is possible to have a continuous monitoring of the product and of the adverse reactions/events that might occur during the administration to the paediatric population.

Furthermore, from a legal perspective, it seems appropriate to clarify that in accordance with Article 20 of Regulation (EC) No 726/2004, the procedure provided therein can be initiated only where the supervisory authorities or the competent authorities of any other Member State are of the opinion that the obligations laid down in Title IV of Directive 2001/83/EC are no longer fulfilled or in case a Member State or the European Commission, as a result of the evaluation of data relating to pharmacovigilance, considers that at least one of the measures envisaged under title IX (Pharmacovigilance) or XI (Supervision and sanctions) of Directive 2001/83/EC must be applied for centrally authorised medicinal products.

5. Regarding the request to proceed with the precautionary suspension of the MA of Beyfortus with immediate effect, pursuant to art. 23 of Regulation (EC) No 726/2004 and the request to adopt enhanced active pharmacovigilance recommendations.

It is unclear why reference is made to Article 23 of Regulation (EC) No 726/2004 to support a request for the precautionary suspension of the MA for Beyfortus.

In accordance with Article 23 of Regulation (EC) No 726/2004, the Agency shall, in collaboration with the Member States, set up, maintain and make public a list of medicinal products that are subject to additional monitoring.
Beyfortus is one of the medicinal products subject to additional monitoring. In principle, all medicines are carefully monitored after they are placed on the EU market. If a medicine is under additional monitoring, this means that it is being monitored even more intensively than other medicines. Furthermore, the MAH of Beyfortus has to submit every year a Periodic safety update reports (PSURs), that is a pharmacovigilance document that contains a comprehensive and critical analysis of the risk-benefit balance of the product, taking into account new or emerging safety information in the context of cumulative information on risk and benefits. This information reported in PSUR is assessed by EMA to determine if there are new risks identified for a medicine and/or if its risk-benefit balance has changed.
As mentioned under point 3, PRAC and CHMP concluded in June 2025 that the benefit-risk balance of medicinal products containing nirsevimab remains unchanged, and they recommended the maintenance of the marketing authorisation.

The precautionary suspension of a marketing authorisation would be justified only in case of serious doubts regarding the safety, quality or efficacy that might potentially have an impact on public health.

In the case at stake, the abovementioned conditions do not occur and for Beyfortus the CHMP has confirmed that the benefit-risk balance remains favourable.

We trust the above addresses your concerns and provides reassurance that EMA carried out its task with the outmost professional diligence.

Kind regards,

Day Francesca

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