



Brussels, 9.6.2023  
C(2023) 3646 final

**COMMISSION IMPLEMENTING DECISION**

**of 9.6.2023**

**granting an authorisation under Regulation (EC) No 1907/2006 of the European Parliament and of the Council to Alexion Pharma International Operations Unlimited Company for a use of 4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated (4-tert-OPnEO)**

(Only the English text is authentic)

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THE EUROPEAN COMMISSION,

Having regard to the Treaty on the Functioning of the European Union,

Having regard to Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC<sup>1</sup>, and in particular Article 64(8) thereof,

Whereas:

- (1) 4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated ('4-tert-OPnEO') is listed in Annex XIV to Regulation (EC) No 1907/2006 and uses of that substance are subject to the authorisation requirement in Article 56(1), point (a), of that Regulation.
- (2) On 28 May 2021, Alexion Pharma International Operations Unlimited Company ('the applicant') submitted an application in accordance with Article 62 of Regulation (EC) No 1907/2006 for authorisation for a use of 4-tert-OPnEO<sup>2</sup>. The use for which authorisation was sought is industrial use of 4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated for virus inactivation in the manufacture of Andexanet alfa for treatment of adult patients treated with a direct factor Xa (FXa) inhibitor when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.
- (3) On 13 June 2022, the Commission received the opinions on the application adopted by the Committee for Risk Assessment (RAC) and by the Committee for Socio-economic Analysis (SEAC) of the European Chemicals Agency<sup>3</sup> and sent to it pursuant to Article 64(5), second subparagraph, of Regulation (EC) No 1907/2006.
- (4) In its opinion, RAC concluded that it is not possible to determine a predicted no-effect concentration for the endocrine disrupting properties of 4-tert-OPnEO for the environment in accordance with Section 6.4 of Annex I to Regulation (EC) No 1907/2006 and that, therefore, 4-tert-OPnEO is a substance for which it is not possible to determine a threshold for the purposes of Article 60(3), point (a), of that Regulation.

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<sup>1</sup> OJ L 396, 30.12.2006, p. 1.

<sup>2</sup> Different names and abbreviations are used to refer to the substance, including 'OPnEO' in the chemical safety report.

<sup>3</sup> <https://echa.europa.eu/documents/10162/d0443daf-2203-397a-5dda-6ef18d6e2c41>

As a result, Article 60(2) of Regulation (EC) No 1907/2006 does not apply to 4-tert-OPnEO and an authorisation may therefore only be granted with respect to that substance under paragraph 4 of that Article.

- (5) RAC noted that risk to the environment cannot be excluded for non-threshold substances, such as 4-tert-OPnEO, even at low exposure levels. Consequently, RAC takes the emissions of the substance as a proxy for the risk.
- (6) In its opinion, RAC concluded that the risk management measures and operational conditions described in the application are not expected to be appropriate and effective in limiting the risk to the environment. RAC noted that the applicant did not provide reliable release estimates, as they were based only on existing experience in similar on-site processes, without further measurements. Moreover, although the applicant ensured that most solid waste and wastewater will be collected for incineration, RAC noted that residual releases are expected from wastewater of subsequent cleaning of the manufacturing equipment from the process. Therefore, RAC recommended that the efficiency of the measures should be verified and improved so as to ensure that releases of 4-tert-OPnEO to the environment are reduced to a level as low as technically and practically possible. Having evaluated RAC's assessment, the Commission agrees with its conclusion and recommendations.
- (7) In its opinion, SEAC had no substantial reservations on the quantitative and qualitative elements of the applicant's assessment of the benefits and risks to the environment associated with the future use of the substance. Taking into account SEAC's assessment, the lack of scientific knowledge at present to quantify or monetise the risk to the environment associated with the future use of 4-tert-OPnEO, the estimated emissions of up to tens of kilograms of the substance per year, the estimated economic benefits due to avoided profit losses at minimum in the order of between tens of thousands of euro and a billion euro over the entire review period, the estimated costs of avoiding the remaining releases of the substance in the order of between hundreds of thousands and tens of millions of euros per kilogram, the qualitatively assessed additional socio-economic benefits of the future use of the substance due to the availability of a specific treatment when reversal of anticoagulation is needed for the treatment of life-threatening or uncontrolled bleeding, as well as any relevant distributional impacts, the Commission concludes that the applicant has demonstrated that the socio-economic benefits of the future use of the substance outweigh the risk to the environment arising from that use.
- (8) A suitable alternative should be safer, available, and technically and economically feasible. Where suitable alternatives are available in the Union, but not technically or economically feasible for the applicant or its downstream users, an authorisation may be granted if the applicant for authorisation submits a substitution plan. An alternative that provides the functionality and level of technical performance necessary for the use for which the authorisation is sought should be considered to be technically feasible.
- (9) In its opinion, SEAC concluded that there were no suitable alternative substances or technologies available for the applicant and in the Union, by the date of adoption of the opinion. The Commission, having evaluated SEAC's assessment and all relevant information available, concludes that further research, development and testing are necessary to assess whether the identified alternatives are compatible with the relevant manufacturing processes while achieving the necessary virus inactivation, for the medicinal product Andexanet alfa currently developed by the applicant. Thus, the Commission considers that it cannot be deemed that the identified alternatives allow

the functionality needed for the use for which the authorisation is sought. Therefore, the Commission agrees with that conclusion and considers that the applicant has discharged its burden of proof in demonstrating the absence of suitable alternatives both in the Union and for the applicant.

- (10) Therefore, having regard to the conditions laid down in Article 60(4) of Regulation (EC) No 1907/2006, it is appropriate to authorise the use of 4-tert-OPnEO described in the application, provided that the risk management measures and operational conditions described in the chemical safety report, as well as the conditions set out in this Decision, are fully applied.
- (11) The Commission has based its assessment on the relevant scientific evidence currently available, as assessed by RAC and SEAC, and, after having carried out a detailed examination, based its conclusions on the existence of a sufficient amount of material and reliable information allowing it to conclude. Nevertheless, additional scientific evidence would allow the Commission to perform its assessment on a more robust or broad evidentiary base in the future. Hence, it is appropriate to require that emission information be generated.
- (12) In its opinion, SEAC recommended that the review period referred to in Article 60(9), point (e), of Regulation (EC) No 1907/2006 should be set until the end of 2030. The Commission agrees with that recommendation, taking into account the relevant elements from RAC's and SEAC's assessments and, in particular, the future estimated emissions, the socio-economic benefits, the lack of suitable alternatives within a shorter timeframe and the research and development efforts undertaken by the applicant.
- (13) The language used to describe the risk management measures and operational conditions in the application for authorisation may be different from the official language of the Member State where the use takes place. Therefore, in order to facilitate supervision and enforcement of compliance with the authorisation, it is appropriate to require the authorisation holder to submit, upon request, a brief summary of those risk management measures and operational conditions to the competent authority of that Member State in an official language of that Member State.
- (14) This Decision does not affect the obligation of the authorisation holder to ensure that a use of a substance does not adversely affect human health or the environment, having regard to the principle set out in Article 1(3) of Regulation (EC) No 1907/2006. Furthermore, this Decision neither affects the obligation of the authorisation holder under Article 60(10) of that Regulation to ensure that the exposure is reduced to as low a level as is technically and practically possible, nor does it affect the obligation of the employer to eliminate or reduce to a minimum risks to the health and safety of workers at work involving hazardous chemical agents in accordance with Article 5(2) of Council Directive 98/24/EC<sup>4</sup>. This Decision does not affect the application of Union law in the area of health and safety at work, in particular Council Directives 89/391/EEC<sup>5</sup>, 92/85/EEC<sup>6</sup>, 94/33/EC<sup>7</sup> and 98/24/EC, or any national binding

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<sup>4</sup> Council Directive 98/24/EC of 7 April 1998 on the protection of the health and safety of workers from the risks related to chemical agents at work (fourteenth individual Directive within the meaning of Article 16(1) of Directive 89/391/EEC) (OJ L 131, 5.5.1998, p. 11).

<sup>5</sup> Council Directive 89/391/EEC of 12 June 1989 on the introduction of measures to encourage improvements in the safety and health of workers at work (OJ L 183, 29.6.1989, p. 1).

occupational limit values which may be stricter than the applicable limit values under Union law.

- (15) This Decision does not affect any obligation to comply with emission limit values or other requirements set in accordance with Directive 2008/50/EC of the European Parliament and of the Council<sup>8</sup> or Directive 2010/75/EU of the European Parliament and of the Council<sup>9</sup>, nor any obligation to comply with emission limit values set to achieve compliance with the environmental quality standards established by Member States in accordance with Directive 2000/60/EC of the European Parliament and of the Council<sup>10</sup> or the environmental quality standards established in Directive 2008/105/EC of the European Parliament and of the Council<sup>11</sup>. Compliance with the provisions of this Decision does not necessarily imply compliance with emission limit values or environmental quality standards under any other provisions of Union law, which may include further or more onerous requirements.
- (16) The measures provided for in this Decision are in accordance with the opinion of the Committee established by Article 133 of Regulation (EC) No 1907/2006,

HAS ADOPTED THIS DECISION:

#### *Article 1*

An authorisation is hereby granted in accordance with Article 60(4) of Regulation (EC) No 1907/2006 for the following use of 4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated (4-tert-OPnEO):

Authorisation number	Authorised use
REACH/23/18/0	Industrial use for virus inactivation in the manufacture of Andexanet alfa for treatment of adult patients treated with a direct factor Xa (FXa) inhibitor when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding

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<sup>6</sup> Council Directive 92/85/EEC of 19 October 1992 on the introduction of measures to encourage improvements in the safety and health at work of pregnant workers and workers who have recently given birth or are breastfeeding (tenth individual Directive within the meaning of Article 16(1) of Directive 89/391/EEC) (OJ L 348, 28.11.1992, p. 1).

<sup>7</sup> Council Directive 94/33/EC of 22 June 1994 on the protection of young people at work (OJ L 216, 20.8.1994, p. 12).

<sup>8</sup> Directive 2008/50/EC of the European Parliament and of the Council of 21 May 2008 on ambient air quality and cleaner air for Europe (OJ L 152, 11.6.2008, p. 1).

<sup>9</sup> Directive 2010/75/EU of the European Parliament and of the Council of 24 November 2010 on industrial emissions (integrated pollution prevention and control) (OJ L 334, 17.12.2010, p. 17).

<sup>10</sup> Directive 2000/60/EC of the European Parliament and of the Council of 23 October 2000 establishing a framework for Community action in the field of water policy (OJ L 327, 22.12.2000, p. 1).

<sup>11</sup> Directive 2008/105/EC of the European Parliament and of the Council of 16 December 2008 on environmental quality standards in the field of water policy, amending and subsequently repealing Council Directives 82/176/EEC, 83/513/EEC, 84/156/EEC, 84/491/EEC, 86/280/EEC and amending Directive 2000/60/EC of the European Parliament and of the Council (OJ L 348, 24.12.2008, p. 84).

The authorisation is granted subject to the risk management measures and operational conditions described in the chemical safety report<sup>12</sup>, as well as to the conditions set out in Article 2.

### *Article 2*

1. The authorisation shall be subject to the conditions set out in paragraphs 2 to 6.
2. The authorisation holder shall carry out a mass balance analysis. This analysis shall be based on the outcome of the measurements referred to in paragraph 4 and shall:
  - (a) be carried out at latest by 3 months as of the start of operation of the facility, and annually thereafter;
  - (b) include details of the calculations carried out;
  - (c) include the assumptions made, if any;
  - (d) include the corresponding release values.
3. The authorisation holder shall optimise the risk management measures and operational conditions on the basis of the results of the analysis referred to in paragraph 2 at the latest by 9 March 2024 so as to reduce the emissions of 4-tert-OPnEO to a level as low as technically and practically possible. The authorisation holder shall document those actions concerning optimisation and make those documents available, upon request, to the competent authority of the Member State where the use takes place.
4. The authorisation holder shall undertake a monitoring programme measuring 4-tert-OPnEO and its principal degradation products in the wastewater prior to its release to the municipal sewage treatment plant. The measurements shall be:
  - (a) carried out for the first time as soon as the facility becomes operational and at least four times per year afterwards, during the time of operation. The initial sampling frequency shall be sufficient to account for daily fluctuations of the discharge. The frequency of the measurements shall be such as to capture the variability in concentrations of 4-tert-OPnEO and its principal degradation products in the wastewater due to changes or operational fluctuations in the process;
  - (b) based on an analytical method capable of adequately characterising 4-tert-OPnEO and its principal degradation products in wastewater with appropriately low limit of quantification;
  - (c) recorded so as to include details of the sampling point, the analytical method, the concentrations detected and the corresponding environmental release values.
5. The authorisation holder shall use the information gathered in accordance with paragraph 4 and related contextual information to review, at least annually, the appropriateness and effectiveness of the risk management measures and operational conditions and, if needed, to introduce measures to further reduce emissions of 4-tert-OPnEO to a level as low as technically and practically possible.

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<sup>12</sup> <https://ec.europa.eu/docsroom/documents/50417>

6. The authorisation holder shall document and keep the information obtained from the measurements referred to in paragraph 4 and the analysis referred to in paragraph 2, as well as the outcome and conclusions of the review and of any measure taken in accordance with paragraph 5, together with the outcome and conclusions of the analysis referred to in paragraph 2. The authorisation holder shall submit that information, upon request, to the competent authority of the Member State where the authorised use takes place.

*Article 3*

1. The review period shall expire on 31 December 2030.
2. The authorisation shall cease to be valid on 31 December 2030 if the authorisation holder has not submitted the review report in accordance with Article 61(1) of Regulation (EC) No 1907/2006 by 30 June 2028.

*Article 4*

Where the authorisation holder submits a review report, that report shall contain the information obtained in accordance with Article 2(3) and (6).

*Article 5*

Upon request, the authorisation holder shall submit a brief summary of the applicable risk management measures and operational conditions, described in the chemical safety report, to the competent authority of the Member State where the authorised use takes place in an official language of that Member State.

*Article 6*

This Decision is addressed to Alexion Pharma International Operations Unlimited Company, College Business & Technology Park, Blanchardstown, D15 R925, Dublin 15, Ireland.

Done at Brussels, 9.6.2023

*For the Commission*

*Thierry BRETON*

*Member of the Commission*

