Committee for Risk Assessment (RAC)

Committee for Socio-economic Analysis (SEAC)

Opinion

on an Application for Authorisation for

4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated

(4-tert-OPnEO)

for

Use of 4-tert-OPnEO in a washing buffer to purify biological APIs (active pharmaceutical ingredients) during the production of Palivizumab and Moxetumomab pasudotox-tdfk

Submitting applicant

Boehringer Ingelheim Pharma GmbH & Co. KG

ECHA/RAC/SEAC: AFA-O-0000006690-73-01/D

Consolidated version

Date: 12/03/2020

Consolidated version of the
Opinion of the Committee for Risk Assessment
and
Opinion of the Committee for Socio-economic Analysis
on an Application for Authorisation

Having regard to Regulation (EC) No 1907/2006 of the European Parliament and of the Council 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (the REACH Regulation), and in particular Chapter 2 of Title VII thereof, the Committee for Risk Assessment (RAC) and the Committee for Socio-economic Analysis (SEAC) have adopted their opinions in accordance with Article 64(4)(a) and (b) respectively of the REACH Regulation with regard to the following application for authorisation:

Applicant(s)[1]	**Boehringer Ingelheim Pharma GmbH & Co. KG** (position in supply chain: downstream) **Boehringer Ingelheim RCV GmbH & Co KG** (position in supply chain: downstream)
Substance ID EC No CAS No	**4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated (in what follows referred to as 4-tert-OPnEO)** **-** **-**
Intrinsic properties referred to in Annex XIV	☐Carcinogenic (Article 57(a)) ☐Mutagenic (Article 57(b)) ☐Toxic to reproduction (Article 57(c)) ☐Persistent, bioaccumulative and toxic (Article 57(d)) ☐Very persistent and very bioaccumulative (Article 57(e)) ☒Other properties in accordance with Article 57(f), please specify: Endocrine disrupting properties - environment
Use title	**Use of 4-tert-OPnEO in a washing buffer to purify biological APIs (active pharmaceutical ingredients) during the production of Palivizumab and Moxetumomab pasudotox-tdfk**
	Other connected uses: not applicable
	Same uses applied for: not applicable
Use performed by	☒ Applicant(s) ☐ Downstream User(s) of the applicant(s)
Use ID (ECHA website)	0138-01

[1] 'Applicant(s)' - includes also 'Authorisation Holder(s)' in case of the review report

Reference number	11-2120808435-57-0001 11-2120808435-57-0002
RAC Rapporteur RAC Co-rapporteur	VAN DER HAAR Rudolf LEINONEN Riitta
SEAC Rapporteur SEAC Co-rapporteur	FIORE-TARDIEU Karine ROUW Aart
ECHA Secretariat	ROGGEMAN Maarten KIVELÄ Kalle SOSNOWSKI Piotr LIOPA Elīna

PROCESS INFORMATION FOR ADOPTION OF THE OPINIONS

Date of submission of the application	11/02/2019
Date of payment, in accordance with Article 8 of Fee Regulation (EC) No 340/2008	10/05/2019
Application has been submitted by the Latest Application Date for the substance and applicant(s) [and their DUs] can benefit from the transitional arrangements described in Article 58(1)(c)(ii).	☒Yes ☐No
Public Consultation on use, in accordance with Article 64(2): https://echa.europa.eu/applications-for-authorisation-previous-consultations	22/05/2019-17/07/2019
Comments received	☐Yes ☒No
Request for additional information in accordance with Article 64(3)	22/05/2019 and 20/06/2019 Link: https://echa.europa.eu/applications-for-authorisation-previous-consultations/-/substance-rev/23317/del/50/col/synonymDynamicField_302/type/asc/pre/5/view
Trialogue meeting	Not held. No new information submitted in public consultation and no need for additional information/discussion on any technical or scientific issues related to the application.
Extension of the time limit set in Article 64(1) for the sending of the draft opinions to the applicant(s)	☐Yes ☒No
The application included all the necessary information specified in Article 62 that is relevant to the Committees' remit.	☒Yes ☐No Comment: none
Date of agreement of the draft opinion in accordance with Article 64(4)(a) and (b)	RAC: 20/09/2019, agreed by consensus.
	SEAC: 20/09/2019, agreed by consensus.
Date of sending of the draft opinion to applicant(s)	06/11/2019

Date of decision of the applicant(s) to comment on the draft opinion, in accordance with Article 64(5)	12/12/2019
Date of receipt of comments in accordance with Article 64(5)	10/01/2020
Date of adoption of the opinion in accordance with Article 64(5)	RAC: 12/03/2020, adopted by consensus.
	SEAC: 11/03/2020, adopted by consensus.
Minority positions	RAC: ☒N/A
	SEAC: ☒N/A

THE OPINION OF RAC

RAC has formulated its opinion on:

- the risks arising from the use applied for,
- the appropriateness and effectiveness of the risk management measures described, as well as
- other available information.

In this application, the applicant did not derive PNEC(s). Therefore, in accordance with Annex I of the REACH Regulation, RAC concluded that for the purposes of the assessment of this application it was not possible to determine PNEC(s) for the endocrine disrupting properties for the environment of the substance.

SEAC concluded that currently there are no technically and economically feasible alternatives available for the applicant(s) with the same function and similar level of performance. Therefore, RAC did not evaluate the potential risk of alternatives.

RAC concluded that the operational conditions and risk management measures described in the application are appropriate and effective in limiting the risk, provided that they are adhered to.

The use applied for may result in up to approximately 45 mg per year emissions of the substance to the environment.

THE OPINION OF SEAC

SEAC has formulated its opinion on:

- the socio-economic factors, and
- the suitability and availability of alternatives associated with the use of the substance as documented in the application, as well as
- other available information.

SEAC took note of RAC's conclusion that it is not possible to determine a PNEC for the endocrine disrupting properties for the environment of the substance in accordance with Annex I of the REACH Regulation.

The following alternatives have been assessed:

- Triton CG-600 (CAS number: 110615-47-9)
- Triton CG-650 (CAS numbers: 110615-47-9 and 68515-73-1)
- Ecosurf EH-6 (CAS number: 64366-70-7)
- Ecosurf EH-9 (CAS number: 64366-70-7)
- Triton CG-110 (CAS numbers: 68515-73-1, 112-30-1 and 111-87-5)
- Triton CG-50 (CAS number: 68515-73-1)
- Tergitol 15-S-9 (no CAS number reported)
  (See Section 4 of the Justifications).

SEAC concluded on the analysis of alternatives that:

- By the Sunset date there are no alternatives available with the same function and similar level of performance that are safer and technically and/or economically feasible for the applicant.
- No substitution plan was submitted.

SEAC concluded on the socio-economic analysis that:

- The expected socio-economic benefits of continued use are at least €45 million (total for 12 years) and other benefits have been assessed qualitatively but have not been quantified.
- Risks to the environment of alternatives have not been quantified. There may be a risk due to the use of an alternative should the authorisation not be granted.

SEAC has no substantial reservations on the quantitative and qualitative elements of the applicant's assessment of the benefits and the risks to the environment associated with the continued use of the substance.

SEAC considered that if an authorisation was refused, the use of the substance could cease altogether.

Furthermore, SEAC considered that, if an authorisation was refused, in the European Union no jobs would be lost.

PROPOSED CONDITIONS AND MONITORING ARRANGEMENTS, AND RECOMMENDATIONS

No conditions or monitoring arrangements are proposed.

REVIEW PERIOD

Taking into account the information provided in the application for authorisation submitted by the applicant(s), a **12-year** review period is recommended for this use.

SUMMARY OF THE USE APPLIED FOR

Role of the applicant(s) in the supply chain	Upstream ☐ [group of] manufacturer[s] ☐ [group of] importer[s] ☐ [group of] only representative[s] ☐ [group of] formulator[s] Downstream ☒ group of downstream users
Number and location of sites covered	2 sites: Biberach (Germany) and Vienna (Austria)
Annual tonnage of Annex XIV substance used per site (or total for all sites)	Biberach (Germany): 0.03-0.05 tonnes per year (production of Palivizumab) Vienna (Austria): 0.10-0.14 tonnes per year (production of Moxetumomab) Total volume: 0.169 tonnes per year[2]
Function(s) of the Annex XIV substance.	The function of 4-tert-OPnEO in the production of two Active Pharmaceutical Ingredients (APIs) (Palivizumab and Moxetumomab) is as a surfactant in a purification process. 4-tert-OPnEO specifically breaks protein-protein, protein-lipid and lipid-lipid associations and thereby facilitates selective removal of hydrophobic contaminants like lipopolysaccharides and hydrophobic host cell proteins - without denaturing the Palivizumab or Moxetumomab proteins.
Type of products (e.g. articles or mixtures) made with Annex XIV substance and their market sectors	Both drugs are custom manufactured for AstraZeneca, a global pharmaceutical company. Palivizumab protects babies at risk of respiratory syncytial virus (RSV) and Moxetumomab is an orphan drug[3] intended for the non-chemotherapy cancer treatment.
Shortlisted alternatives discussed in the application	Alternative substances considered: • Triton CG-600 (CAS number: 110615-47-9) • Triton CG-650 (CAS numbers: 110615-47-9 and 68515-73-1) • Ecosurf EH-6 (CAS number: 64366-70-7) • Ecosurf EH-9 (CAS number: 64366-70-7) • Triton CG-110 (CAS numbers: 68515-73-1, 112-30-1 and 111-87-5)

[2] The applicants stated that these values reflect the maximum amount of use of 4-tert-OPnEO at each site of Boehringer Ingelheim allowing for a safety tolerance in case that one campaign needs to be repeated.

[3] An orphan medicine is defined as a *"medicine for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition that is rare (affecting not more than five in 10,000 people in the European Union) or where the medicine is unlikely to generate sufficient profit to justify research and development costs"*. Source: https://www.ema.europa.eu/en/glossary/orphan-medicine

	• Triton CG-50 (CAS number: 68515-73-1) • Tergitol 15-S-9 (no CAS number reported) Alternative technologies considered: none
Annex XIV substance present in concentrations above 0.1% in the products (e.g. articles) made	☐Yes ☒No ☐Unclear ☐Not relevant
Releases to the environmental compartments	☐Air ☒Water ☐Soil ☐None
The applicants have used the PNEC recommended by RAC	☐Yes ☐No ☒Not relevant
All endpoints listed in Annex XIV were addressed in the assessment	☒Yes ☐No if 'No' – which endpoints are not addressed
Adequate control demonstrated by applicant(s) for the relevant endpoint(s)	☐Yes ☐No ☒Not Applicable – non-threshold substance
Level of (combined, daily) exposure/release used by applicant(s) for risk characterisation	<u>Release</u> Water: Despite the collection of 4-tert-OPnEO containing wastewater from the first rinsing steps, residual releases of 4-tert-OPnEO are estimated to occur from subsequent rinsing procedures of tanks, separators, and chromatography columns and are estimated to be as follows: - In Biberach (Germany): 0.01-0.03 g/year - In Vienna (Austria): 0.005-0.015 g/year - Total release: 0.015-0.045 g/year Air: 0 g/year (emissions to air are considered to be negligible, because of the relatively low vapour pressure of the substance of < 0.01 hPa at 20 °C) Soil: 0 g/year (no emissions to soil is expected, because sludge is drained and incinerated)

Risk Characterisation	Environmental compartments: The applicants did not attempt to derive PNECs or RCRs. The CSR describes how the OCs and RMMs in the ES prevent or minimise releases to the environment as far as technically and practically possible (with the view to minimising the likelihood of adverse effects). The applicants consider that risk arising from the use applied for is negligible due to the risk management measures applied (incineration of all 4-tert-OPnEO contaminated waste and wastewater) effectively preventing the release of 4-tert-OPnEO to the environment.
Applicants are seeking authorisation for the period of time needed to finalise substitution (‘*bridging application*’)	☐Yes ☒No ☐Unclear
Review period argued for by the applicant(s) (length)	12 years
Most likely Non-Use scenario	Temporary cease of the production of the drugs followed by a substitution with non-specified alternative substance.
Applicant(s) conclude(s) that benefits of continued use outweigh the risks of continued use	☒Yes ☐No ☐Not Applicable – threshold substance with adequate control
Applicant’s(s’) benefits of continued use	- Avoided cost of R&D and market approval of €45 million (total for 12 years). - Profit losses are not significant according to the applicants.
Society’s benefits of continued use	Availability of medication to respiratory syncytial virus and for non-chemotherapy cancer treatment
Monetised health impact on workers	Not relevant
Distributional impacts if authorisation is not granted	Patients benefiting from the medication to respiratory syncytial virus and for non-chemotherapy cancer treatment would be highly affected.
Job loss impacts if authorisation is not granted	Job losses are not significant according to the applicants.

SUMMARY OF RAC AND SEAC CONCLUSIONS[4]

1. Operational Conditions and Risk Management Measures

1.1. Conclusions of RAC

Conclusion for environment

Since all solid waste, which had been in contact with 4-tert-OPnEO, is collected and disposed of as waste for incineration and the relevant wastewater (e.g. first rinsing water) is collected for incineration, no shortcomings to the operational conditions (OCs) and risk management measures (RMMs) have been identified.

Are the OCs/RMMs in the Exposure Scenario appropriate and effective in limiting the risk?

☒Yes ☐No

Does RAC propose additional conditions related to the operational conditions and risk management measures for the authorisation?

☐Yes ☒No

Does RAC propose monitoring arrangements related to the operational conditions and risk management measures for the authorisation?

☐Yes ☒No

Does RAC make recommendations related to the operational conditions and risk management measures for the review report?

☐Yes ☒No

2. Exposure Assessment

Conclusions of RAC

RAC considers that the release estimates provided by the applicants are appropriate. RAC did not identify shortcomings in the methodology used by the applicants to estimate release (modelling approach), the assumptions chosen in the modelling of releases, or representativeness of the release estimates, that would invalidate this conclusion.

Does RAC propose additional conditions[5] related to exposure assessment for the authorisation?

☐Yes ☒No

[4] The numbering of the sections below corresponds to the numbers of the relevant sections in the Justifications.

[5] Conditions can be proposed where RCR is > 1, OCs and RMMs are not appropriate and effective, risk is not adequately controlled, minimisation of emissions is not demonstrated.

Does RAC propose monitoring arrangements related to exposure assessment for the authorisation?

☐Yes ☒No

Does RAC make recommendations related to exposure assessment for the review report?

☐Yes ☒No

3. Risk Characterisation

Conclusions of RAC

The applicants have treated 4-tert-OPnEO as a non-threshold substance and did not attempt to derive PNECs or RCRs. This approach is in line with RAC's paper *"Risk-related considerations in applications for authorisation for endocrine disrupting substances for the environment, specifically OPnEO and NPnEO"*, adopted at RAC-43[6] and RAC's conclusion on this issue at RAC-50.

Based on the OCs & RMMs in the ES, notably the use of 4-tert-OPnEO in closed systems and incineration of solid and liquid wastes, RAC is of the view that the applicants have demonstrated that releases to environmental compartments have been prevented or minimised as far as technically and practically possible (with the view to minimising the likelihood of adverse effects).

The use applied for may result in up to approximately 45 mg per year emissions of 4-tert-OPnEO to the environment. Risks to the environment cannot be excluded for non-threshold substances even at low exposure levels. However, in this case, RAC is of the view that the likelihood of adverse effects can be considered negligible (i.e. nearing zero).

4. Analysis of alternatives

What is the amount of substance that the applicant uses per year for the use applied for?

0.169 tonnes per year.

Are there alternatives with the same function and similar level of performance that are technically and economically feasible to the applicant before the Sunset Date?

☐Yes ☒No

Has the applicant submitted a substitution plan?

☐Yes ☒No

Does SEAC propose any additional conditions or monitoring arrangements related to the assessment of alternatives for the authorisation?

☐Yes ☒No

6 https://echa.europa.eu/documents/10162/13637/npneo_and_opneo_for_agreement_final_en.pdf/026cbafc-6580-1726-27f3-476d05fbeef0

Does SEAC make any recommendations to the applicant(s) related to the content of the potential review report?

☐Yes ☒No

The alternatives identified by the applicant are not suitable by the sunset date.

5. Benefits and risks of continued use

Has the applicant adequately assessed the benefits and the risks of continued use?

Conclusions of SEAC:

☒Yes ☐No

SEAC has no substantial reservations on the quantitative and qualitative elements of the applicant's assessment of the benefits and the risks to the environment associated with the continued use of the substance.

6. Proposed review period for the use

☐ 4 years

☐ 7 years

☒ 12 years

☐ Other – … years

7. Proposed additional conditions for the authorisation

RAC

Additional conditions:

For the environment ☐Yes ☒No

SEAC

Additional conditions: ☐Yes ☒No

8. Proposed monitoring arrangements for the authorisation

RAC

Monitoring arrangements:

For the environment ☐Yes ☒No

SEAC

Monitoring arrangements ☐Yes ☒No

9. Recommendations for the review report

RAC

For the environment	☐Yes	☒No

SEAC

AoA	☐Yes	☒No
SP	☐Yes	☒No
SEA	☐Yes	☒No

10. Applicant(s) comments on the draft opinion

Has the applicant commented the draft opinion?

☒Yes ☐No

Has [Have] action(s) been taken resulting from the analysis of the applicants' comments?

☒Yes ☐No

JUSTIFICATIONS

0. Short description of use

Boehringer Ingelheim Pharma and Boehringer Ingelheim RCV applied for the use of 4-tert-OPnEO in the production of two therapeutic proteins, Palivizumab and Moxetumomab pasudotox–tdfk (hereafter Moxetumomab). Palivizumab and Moxetumomab are produced by mammalian cell culture processing (murine myeloma NS0 cells) and fermentation (*E. Coli*), respectively. The site in Biberach (Germany) uses 0.03-0.05 tonnes per year in the production of Palivizumab. The site in Vienna (Austria) uses 0.10-0.14 tonnes per year in the production of Moxetumomab. The total volume of 4-tert-OPnEO used is 0.169 tonnes per year.

Palivizumab (also sold under the name of Synagis®) protects babies at risk of respiratory syncytial virus (RSV) and Moxetumomab is an orphan drug intended for the non-chemotherapy cancer treatment.

Both drugs are custom manufactured for AstraZeneca, a global pharmaceutical company.

0.1 Description of the process in which Annex XIV substance is used

4-tert-OPnEO is used in closed processes in accordance with the use conditions set out in the CSR. 4-tert-OPnEO is purchased and added to washing buffer in a concentration of up to 1% w/v. After removal of the final product, the washing buffer is collected and disposed as waste (incineration). 4-tert-OPnEO is not present in the final products (Palivizumab and Moxetumomab).

Supply, storage and quality analysis

4-tert-OPnEO (Triton X-100, CAS No 9036-19-5, Merck) is supplied in 2.5 l glass bottles. After receipt, a quality sample of the batch is taken and analysed. Samples are taken inside a fume cupboard. After analysis, the sample is collected in a specific wastewater tank. Solid waste (equipment used for taking samples are one-way articles) contaminated with 4-tert-OPnEO is collected in a bin and disposed as hazardous waste.

After approval, the 4-tert-OPnEO bottles are taken to the warehouse. The entire process is performed under strict GMP rules with no release to the environment. When containers are rinsed, all wastewater is collected as hazardous waste.

All liquid and solid hazardous waste containing 4-tert-OPnEO is handed over to a certified waste contractor for incineration.

Preparation of wash buffer

At both sites, the buffer containing 4-tert-OPnEO is prepared by manually filling 4-tert-OPnEO into a mixing tank. The buffer solution is subsequently stirred and filtered.

The production is strictly controlled with separate material and personnel air locks. Only authorized personnel can enter the area.

Unused buffer and wastewater containing 4-tert-OPnEO is collected in a specific wastewater tank and disposed through a certified waste contractor and incinerated.

*Use of 4-tert-OPnEO during wash step in the **primary recovery** of crude API (Moxetumomab only, Vienna site)*

After fermentation the cells (E. Coli) are harvested, cell membranes are disrupted by homogenisation and inclusion bodies[7] are harvested by centrifugation. The obtained inclusion body slurry is diluted using an aqueous washing buffer containing 4-tert-OPnEO. The diluted slurry is centrifuged. This wash step is repeated using buffer solution without 4-tert-OPnEO. The inclusion body slurry may be isolated or directly processed in the next step. Solid waste and wastewater containing 4-tert-OPnEO is collected, including the first wash buffer without 4-tert-OPnEO, and handed over to a certified waste disposal contractor for incineration.

*Use of 4-tert-OPnEO during the **chromatographic step** (Palivizumab; Biberach site and Moxetumomab; Vienna site)*

During the chromatographic purification steps, the API (protein) is captured by the resin. The resin is washed with a buffer containing a low level of 4-tert-OPnEO in order to strip host cell proteins (HCPs) and endotoxins from the chromatographic resin, while the final API remains bound to the resin. Afterwards the wash step is repeated using buffer without 4-tert-OPnEO. Solid waste and wastewater containing 4-tert-OPnEO is collected, including the first wash buffer without 4-tert-OPnEO, and handed over to a certified waste disposal contractor for incineration.

0.2 Key functions and properties provided by the Annex XIV substance

The function of 4-tert-OPnEO is as a surfactant in a purification process. 4-tert-OPnEO specifically breaks protein-protein, protein-lipid and lipid-lipid associations and thereby facilitates selective removal of hydrophobic contaminants like lipopolysaccharides and hydrophobic host cell proteins - without denaturing the Palivizumab or Moxetumomab proteins[8].

0.3 Type(s) of product(s) made with Annex XIV substance and market sector(s) likely to be affected by the authorisation

Boehringer Ingelheim uses 4-tert-OPnEO within the purification of producing Palivizumab and Moxetumomab, two biological APIs (or drugs), at its sites in Biberach (Germany) and Vienna (Austria). The authorities have approved the biopharmaceuticals and the specific processes used to manufacture them, under Directive 2001/83/EC, Regulation (EC) No 726/2004 and the US Federal Food, Drug, and Cosmetic Act.

[7] The term “inclusion bodies” refers to metabolically inactive materials within the cytoplasm or nucleus of a cell; in this specific case it refers to inactive, unfolded forms of the target VH-PE38 or VL protein chain within the cytoplasm. Moxetumomab is made of the protein chains VH-PE38 and VL.

[8] Moxetumomab is a recombinant protein immunotoxin composed of the Fv portion of disulphide linked affinity matured light (VL) and heavy (VH) antibody chain of the mouse anti-CD22 monoclonal antibody RFB4 fused to PE38 toxin.
Palivizumab is a humanized monoclonal antibody.

1. Operational Conditions and Risk Management Measures

1.1 Environment

The applicants presented one exposure scenario (ES1 Use of protein wash buffer) with one environmental contributing scenario (ECS) for each site:

- ES1-CS1 Biberach (includes storage, internal transport, buffer preparation, API cleaning and wastewater treatment) - ERC4
- ES1-CS2 Vienna (includes storage, internal transport, buffer preparation, API cleaning and wastewater treatment) - ERC4

A summary of the OCs & RMMs in the environmental contributing scenarios is provided below. The detailed conditions of use are available from section 9.2.1 and 9.2.1 of the CSR.

No worker contributing scenarios are presented, as the scope of the CSR is limited on the environmental risk of 4-tert-OPnEO.

No contributing scenario for the service life is provided because 4-tert-OPnEO is stated not to be present in the final products (Palivizumab and Moxetumomab). 4-tert-OPnEO is stated not to bind to the active pharmaceutical ingredients. For Palivizumab, the applicants have consistently met the specification for Drug Substance release requiring that the concentration of 4-tert-OPnEO be below 300 ng/mg protein (0.03 % w/w or 300 ppm). Four consecutive Moxetumomab batches were tested for residual 4-tert-OPnEO and all results were below the limit of detection of 0.1 µg/ml (about 0.1 ppm).

Operational conditions

The operational conditions are presented in Table 1.

Table 1 Summary of operational conditions

	Biberach	Vienna
Volume used per year	0.03-0.05 t/year	0.10-0.14 t/year
Number of days of release per year	10-20 (1-5 campaigns/year 12-14 batches/campaign)	1-4 days for the wash step in the primary recovery and 1-4 days for the chromatographic purification step
Concentration of 4-tert-OPnEO in washing buffer	≤ 1 % (w/v)	≤ 1 % (w/v)
Daily release 4 tert-OPnEO	1.39 mg/day chromatographic purification step	0.133 mg/day during primary recovery and 4.148 mg/day during the chromatographic purification step
Temperature	room temperature (15-30 °C) chromatographic purification step	≤ 12 °C during primary recovery and room temperature (ca. 22 ± 3 °C) during the chromatographic purification step

Technical and organisational conditions and measures

- Production under strictly controlled conditions with separate material and personnel air locks.
- Production and transfer of fluids containing 4-tert-OPnEO takes place under rigorous containment in closed equipment.
- Processes have been re-engineered to allow for the collection of wastewater in containers to prevent discharging into the sewage system.
- An emergency plan is available for spill incidents for inside as well as outside of the facilities. All waste out of a spill event will be disposed of and incinerated by a certified contractor.
- A continuous inventory check of the raw material volume of 4-tert-OPnEO is in place, tracking the volume of incoming and used 4-tert-OPnEO. If the material balance is off by more than 3% alarms are set off by issuing a deviation report describing a root cause analysis and corrective actions
- A preventive maintenance program is in place for the tanks, pipes and hoses regarding integrity and leaks.
- Integrated EHS management systems are in place at Biberach (ISO 50001; ISO 14001, and ISO 45001) and Vienna (ISO 14001 and ISO 45001).
- Incoming inspection is performed to confirm that the raw materials meet the required specifications. This takes place in cleanroom class C and class D areas[9] to prevent contamination of the raw material.
- The processes are performed in compliance with the good manufacturing practise (GMP) of the pharmaceutical industry[10].
- Standard Operation Procedures (SOPs) are in place for all activities.
- Annual training is provided to all involved operators.
- The access to warehouse, laboratory and manufacturing areas is strictly controlled to prevent unauthorised access (chip card system).

Waste management

Both sites (Biberach and Vienna) have contracted certified waste disposal companies for handling solid and liquid waste that could have been in contact with the 4-tert-OPnEO.

All solid waste (filter capsule, single use articles for weighing and transport like measuring beakers, funnels, single use hoses in contact with 4-tert-OPnEO containing buffers, filters, etc.), which had been in contact with 4-tert-OPnEO, is collected in a bin and disposed as waste for incineration. The applicant stated that there is no relevant emission to the environment via this route.

All 4-tert-OPnEO-containing wastewater is collected for incineration, this includes rinsing water from the first rinsing steps of equipment that has been in contact with 4-tert-OPnEO (e.g. tanks, chromatography columns, transfer pipes):

- At the Biberach site the 4-tert-OPnEO-contaminated wastewater is collected and transferred into an external 25 000 l tank. This transfer is completely automated and in a closed system. The transfer from the external tank into the tank truck from the disposal company takes place in a closed transfer system. During transfer, the truck is

[9] Class C and class D refer to the EU GMP directive and are comparable to the ISO classes 7 and 8 of DIN EN ISO 14644-1, respectively.

[10] All active substances should be manufactured in accordance with the principles and guidelines of good manufacturing practice for active substances. The principles are laid down in EU legislation and are complemented with guidelines, see also https://ec.europa.eu/health/documents/eudralex/vol-4_en

standing on a drain pan. In case of a spill, potential 4-tert-OPnEO is collected in the pan and re-pumped into the external tank.
- At the Vienna site 4-tert-OPnEO-contaminated wastewater is collected and transferred into fixed tanks (primary recovery) and mobile tanks (chromatography step). Transfer from fixed tanks to the tank truck takes place under similar conditions as at Biberach. The content of the mobile tanks (i.e. single use waste bags) is gravity-fed to an IBC (Intermediate Bulk Container). The IBC is collected by the waste disposal contractor.

Residual releases occur via the waste water treatment plant (WWTP) originating from residual amounts of 4-tert-OPnEO present in subsequent rinsing steps (e.g. tanks, transfer pipes, separators and chromatography columns):

- At the Biberach site wastewater with residual 4-tert-OPnEO from subsequent rinsing steps goes to the on-site WWTP (activated sludge). Sludge is drained and sent offsite for incineration.
- At the Vienna site wastewater with residual 4-tert-OPnEO from subsequent rinsing steps is routed to the municipal WWPT in Vienna, when all chemical requirements (temperature, pH-value, thresholds for organic and inorganic contaminants, inactivation of genetically modified organisms) for the sewer are fulfilled. Sludge from the municipal WWTP in Vienna is drained and incinerated.

Section 9.2.1 and 9.2.2 of the CSR give a detailed description of the amounts of wastewater generated in each process step, and the fraction that is collected for incineration or is routed to the municipal WWTP, respectively.

Table 2 Environmental RMMs - summary

Compartment	RMM	Stated Effectiveness
Air	Closed systems	Not applicable (closed systems and relatively low volatility)
Water	Mainly: incineration of solid and liquid waste	No residual releases assumed from waste water that is collected for incineration. Residual release rates from waste water of subsequent rinsing steps, see Table 3.
Soil	Sludge from WWTP is incinerated	Not applicable

1.2 Discussion on OCs and RMMs and relevant shortcomings or uncertainties

Since all solid waste, which had been in contact with 4-tert-OPnEO, is collected and disposed of as waste for incineration and the relevant wastewater (e.g. first rinsing water) is collected for incineration, no shortcomings to the operational conditions (OCs) and risk management measures (RMMs) have been identified.

1.3 Conclusions on OCs and RMMs

Overall conclusion

Are the operational conditions and risk management measures appropriate[11] and effective[12] in limiting the risk for workers, consumers, humans via environment and / or environment?

Workers	☐Yes	☐No	☒Not relevant
Consumers	☐Yes	☐No	☒Not relevant
Humans via Environment	☐Yes	☐No	☒Not relevant
Environment	☒Yes	☐No	☐Not relevant

2. Exposure assessment

2.1. Environmental exposure

Water

Since solid waste and wastewater, with the exception of the subsequent rinsing steps, is collected for incineration, the environmental exposure assessment presented by the applicants is based on the residual release of these subsequent rising steps.

The applicants used site-specific release and exposure modelling. The volume of wastewater that is collected for incineration or that is released to the WWTP is estimated per relevant production step and per site. The release fraction to the WWTP was estimated on the basis of the site-specific processes. The main assumptions used in estimating the residual releases are (details provided in Annex I to the CSR):

- Process pipelines are rinsed after use of 4-tert-OPnEO (except one-way silicone transfer pipes at the Vienna site which are collected for incineration), and rinse-water is collected for incineration. Potential remaining 4-tert-OPnEO concentrations are considered negligible (no release is assumed).
- Based on the film thickness, the tank (or separator) surface and the concentration of 4-tert-OPnEO, the residual 4-tert-OPnEO after emptying the tank is calculated. Following application of the dilution (removal) effectiveness of the rinsing step to this volume the release is calculated:
    - A worst-case film thickness of 0.1 mm is assumed for the liquid film that remains in tanks after draining all liquids (justification provided).
    - Tanks are never completely filled with 4-tert-OPnEO-containing solutions. However, as a worst-case, it is assumed that the complete inner surface of the tank is contaminated.
    - For the cleaning of tanks and separators, a dilution effectiveness of 99.9 % is assumed (justification provided in Annex 1 of the CSR);
- For the chromatography column, the approach is similar. A dilution effectiveness of 99 % is assumed (justification provided in Annex 1 of the CSR).

[11] 'Appropriateness' – relates to the following of the principles of the hierarchy of controls in application of RMMs and compliance with the relevant legislation.
[12] 'Effectiveness' – evaluation of the degree to which the RMM is successful in producing the desired effect – exposure / emissions reduction, taking into account for example proper installation, maintenance, procedures and relevant training provided.

As shown in Table 3, the OCs & RMMs, in particular containment and incineration of waste, result in annual release estimates of 4-tert-OPnEO below 45 mg per year (a release factor of $< 10^{-6}$ and an annual use of 169 kg per year).

The applicants attempted to measure the concentration of 4-tert-OPnEO in wastewater samples from the Vienna site[13] according to DIN EN ISO 18857-2: 2012-01. According to the applicant the method only allows for a quantitation of 4-tert-OPnEO for concentrations ≥ 500 ng/L. No other suitable method with a lower LOQ is available yet. The applicants reported that, due to matrix effects, in 50 % of all analysed samples both 4-tert-OPnEO and the internal standard (nonylphenol) could not be identified and/or quantified. Therefore, the applicants did not consider the results reliable and did not include the data in the assessment. For the same reasons, collected and stored wastewater samples from Biberach have not been analysed[14].

Table 3 Summary of environmental emissions of 4-tert-OPnEO

Release route	Release factor	Release per year	Release estimation method and details
Water	$< 1 \times 10^{-6}$	Biberach: 0.01-0.03 g/year Vienna: 0.005-0.015 g/year Total: 0.015-0.045 g/year	Release fraction to the WWTP was estimated (modelled) on the basis of the site-specific processes
Air	0	0	The applicants state that the emissions to air are negligible, because of the low vapour pressure of the substance of < 0.01 hPa at 20 °C
Soil	0	0	The applicants state that there are no emissions to soil is expected, because sludge is drained and incinerated

2.2. Discussion of the information provided and any relevant shortcomings or uncertainties related to exposure assessment

The potential for release is low as a result of the use of 4-tert-OPnEO in closed systems and incineration of solid and liquid wastes. RAC considers that the methodology for assessing the release from residual releases to water is appropriate. The modelled release factors are based on site-specific input parameters, representing worst case scenarios. All parameters are transparently reported and adequately justified. The estimates can be considered to be representative and are not likely to underestimate release.

RAC notes that the applicants made an unsuccessful attempt to measure the concentration of 4-tert-OPnEO in wastewater samples. Ideally, reliable measured data would have been available to corroborate the modelled release estimates. However, RAC acknowledges the

[13] The expected concentration of the effluent released from the primary recovery at Vienna can be calculated as 4 ng/L (based on 0.1326 mg release per campaign divided by 33 000 L the amount of wastewater per campaign) and for the chromatography step 9 116 ng/L (4.148 mg release per campaign divided by 455 L the amount of wastewater per campaign).

[14] The modelled concentration in the effluent of the waste water treatment plant is 0.93 ng 4-tert-OPnEO/L.

challenges of measuring 4-tert-OPnEO in waste water and considers the lack thereof, in this case, not as a shortcoming in the assessment. Measurement data may be included in a possible review report in order to corroborate the modelled release estimates and to demonstrate the effectiveness of the OCs and RMMs in place.

As a result of the relatively low vapour pressure of 4-tert-OPnEO[15] and the level of containment in the processes (largely in closed systems), RAC concurs that releases to air are expected to be negligible. Similarly, RAC agrees that direct releases to soil are not likely. Considering that the sludge from the on-site WWTP of the Biberach site and the municipal WWTP in Vienna is stated to be drained and incinerated, RAC agrees that also indirect releases to soil are not expected.

RAC did not assess the predicted environmental concentrations (PECs) provided by the applicants since 4-tert-OPnEO is treated as a non-threshold substance for its endocrine disrupting properties for the environment and therefore no appropriate PNECs or other benchmark values such as EQSs are available for comparison.

2.3. Conclusions on exposure assessment

RAC considers that the release estimates provided by the applicants are appropriate. RAC did not identify shortcomings in the methodology used by the applicants to estimate release (modelling approach), the assumptions chosen in the modelling of releases, or representativeness of the release estimates, that would invalidate this conclusion.

3. Risk characterisation

The applicants have treated 4-tert-OPnEO as a non-threshold substance and did not attempt to derive PNECs or RCRs. This approach is in line with RAC's paper *"Risk-related considerations in applications for authorisation for endocrine disrupting substances for the environment, specifically OPnEO and NPnEO"*, adopted at RAC-43 and RAC's conclusion on this issue at RAC-50.

Based on the OCs & RMMs in the ES, notably the use of 4-tert-OPnEO in closed systems and incineration of solid and liquid wastes, RAC is of the view that the applicants have demonstrated that releases to environmental compartments have been prevented or minimised as far as technically and practically possible (with the view to minimising the likelihood of adverse effects).

The use applied for may result in up to approximately 45 mg per year emissions of 4-tert-OPnEO to the environment. Risks to the environment cannot be excluded for non-threshold substances even at low exposure levels. However, in this case, RAC is of the view that the likelihood of adverse effects is negligible (i.e. nearing zero).

[15] The applicant reports that 4-tert-OPnEO has a vapour pressure of < 0.01 hPa at 20 °C (0.001 kPa at 20 °C). As the vapour pressure is below 0.01 kPa, 4-tert-OPnEO is not a 'volatile organic compound' as defined by the Industrial Emissions Directive (Directive 2010/75/EU): *"'volatile organic compound' means any organic compound as well as the fraction of creosote, having at 293.15 K a vapour pressure of 0,01 kPa or more, or having a corresponding volatility under the particular conditions of use".*

4. Analysis of Alternatives

What is the amount of substance that the applicant uses per year for the use applied for?

0.169 tonnes per year.

4.1. Summary of the Analysis of Alternatives by the applicant(s) and of the comments received during the public consultation and other information available

The applicants reviewed the scientific and patent literature and consulted suppliers of surfactants to identify alternatives. As EU and other regulations on the marketing of pharmaceutical products require that changes in the manufacturing process should not affect the quality of a drug, the focus of the applicants' review was on alternatives for which information was available regarding their use in the purification of therapeutic proteins.

The applicants discarded alternatives that are not considered suitable based on potential risks to workers, environment or patients, as well as alternatives whose effect on product quality are unknown. A short list of seven alternatives were assessed in terms of their technical and economic feasibility, availability and reduction of overall risk. The shortlisted potential alternatives are:

- Triton CG-600 (CAS number: 110615-47-9)
- Triton CG-650 (CAS numbers: 110615-47-9 and 68515-73-1)
- Ecosurf EH-6 (CAS number: 64366-70-7)
- Ecosurf EH-9 (CAS number: 64366-70-7)
- Triton CG-110 (CAS numbers: 68515-73-1, 112-30-1 and 111-87-5)
- Triton CG-50 (CAS number: 68515-73-1)
- Tergitol 15-S-9 (no CAS number reported)

The assessment of technical feasibility summarises the information available to the applicants on the potential impacts of substituting on the products' quality. The applicant uses 4-tert-OPnEO as a surfactant in a purification process. The challenge is to choose an alternative surfactant which can disrupt the unwanted interactions without disrupting interactions within the drug proteins, which could lead to product quality changes (such as size variants, charge variants, oxidation variants, deamidation variants and increased levels of impurities).

The applicants assessed the economic feasibility of alternatives in terms of costs related to R&D and obtaining market approval. The cost of using the alternative substance (e.g. in terms of price for raw material) is insignificant according to the applicants.

The AoA describes the steps needed to obtain market approval. The applicant estimates the costs related to R&D and for obtaining market approval for the changes in the current way of producing the two drugs to be around €14 million for the orphan drug Moxetumomab and €31 million for Palivizumab (total for 12 years). According to the applicant, the substitution process requires at least 5.5 years for Moxetumomab and at least 10.5 years for Palivizumab.

The applicants indicate that during the review period they do not plan to substitute 4-tert-OPnEO for the two drugs manufactured. According to the applicant, the R&D on alternatives to 4-tert-OPnEO is currently at an early stage, but as both the applicant and AstraZeneca intend to avoid 4-tert-OPnEO in new pharmaceutical products (AstraZeneca is currently developing a next generation biologic treatment -MEDI8897- for RSV with a manufacturing process that does not use 4-tert-OPnEO). Further work of substituting OPE in the current Palivizumab production process will only be started if it would become clear that the new drug will not be able to replace Palivizumab in all cases.

No comments were received in the public consultation.

4.2. Risk reduction capacity of the alternatives

Would the implementation of the short-listed alternative(s) lead to an overall reduction of risks?

☐Yes

☐No

☒Not applicable

As no technically and economically feasible alternatives are available before the Sunset Date, RAC did not evaluate the information provided by the applicants regarding the potential for risk reduction due to transition to alternatives[16].

4.3. Availability and technical and economic feasibility of alternatives for the applicant

Are there alternatives with the same function and similar level of performance that are technically and economically feasible to the applicant before the Sunset Date?

☐Yes ☒No

SEAC's evaluation / view on the availability and technical and economic feasibility of alternatives for the applicant

SEAC considers that the approach by the applicant to identifying and assessing alternatives allows for conclusions on the availability and suitability of alternatives. In SEAC's view, the applicant's assessment is sufficient to conclude on the availability of alternatives. SEAC notes that the applicants do not commit to substitute the use of 4-tert-OPnEO in the production of the drugs covered by this application during the review period, but intend to avoid use of the substance for the development of new drugs.

[16] The applicants compared the classification of alternatives and 4-tert-OPnEO, and compared RCRs calculated based on PECs and PNECs for the shortlisted alternatives and for 4-tert-OPnEO. The applicants stressed that the use of an indicative PNEC value for 4-tert-OPnEO and calculation of an RCR was only to illustrate the relative risks that would result from substitution. The applicants considered 4-tert-OPnEO is a non-threshold substance and followed the socio-economic route. The applicants concluded that implementation of the short-listed alternatives could result in a reduction of the overall risk to human health and the environment assuming that wastewater containing 4-tert-OPnEO were discharged to the environment. The applicants noted that however the environmental risk from 4-tert-OPnEO is negligible since wastewater is collected for incineration: the applicants considered that the lowest risk for the environment is the scenario of continued use of 4-tert-OPnEO (contaminated wastewater is collected for incineration, whereas this is not assumed to be the case when using the alternatives).

SEAC considers that the assessment by the applicant demonstrates that suitable alternatives are not available for the applicant before the sunset date due to the required market approval, need to ensure the performance of any potential alternatives, and the costs associated with the substitution process. Even if technically feasible alternatives could be developed during the requested review period of 12 years (for Palivizumab for which the substitution process requires at least 10.5 years) and even during a 7-year review period (for Moxetumomab for which the substitution process requires at least 5.5 years), the costs related to R&D and for obtaining market approvals are prohibitively high so that SEAC considers the alternatives not to be economically feasible for the applicant. In the case of Palivizumab, profitability is expected to drop when competitive drugs come on the market. Moxetumomab as an orphan drug has by its very nature a very low profitability and has only been recently launched in the market. Therefore, to the applicant high R&D re-investments in both products seem unreasonable in view of commitment of resources for the development of other products. SEAC considers that this situation is unlikely to change over the next decade as the approval requirement and high costs related to that are certain to remain applicable.

4.4. Substitution activities / plan

In view of the unfavourable cost-effectiveness of substitution (see section 5), the applicants do not consider substitution as a viable option and do not plan to substitute the use of 4-tert-OPnEO in the production of the two drugs covered by this application as long as they are produced. However, in all ongoing and new drug substance developments they are carrying out research efforts towards finding alternatives for 4-tert-OPnEO.

Has the applicant submitted a substitution plan?

☐Yes ☒No

The applicants have not submitted a separate substitution plan because they do not intend to substitute. However, in section 3.2.1 of the SEA document in the application for authorisation the applicant presented a roadmap with information about the development activities that need to be performed, with detailed validation process steps and timelines, if substitution of 4-tert-OPnEO would be pursued.

4.5. Conclusions on the analysis of alternatives

The alternatives identified by the applicant are not suitable by the sunset date.

5. Benefits and risks of continued use

Have the applicants adequately assessed the benefits and the risks of continued use?

☒ Yes

☐ No

5.1. Environmental impacts of continued use

According to the applicants, the risk management measures currently implemented at the applicants' site eliminate potential releases of 4-tert-OPnEO into the environment and prevent endocrine disrupting effects on any species potentially exposed to it in their natural habitat.

RAC confirms that the applicant has demonstrated that releases to environmental compartments have been prevented or minimised as far as technically and practically possible and that adverse effects are negligible (nearing zero). Therefore, SEAC concludes that, although in principle impacts on the environment cannot be excluded, these are expected to be negligible.

5.2. Benefits of continued use

Non-use scenario

According to the applicants, an authorisation for the continued use of 4-tert-OPnEO is necessary for the production of two drugs. The use of the substance applied for has a direct effect on the final product quality of these drugs and consequently they could not be placed on the market without using 4-tert-OPnEO in the production.

The applicants assessed two non-use scenarios (NUS) in their application: 1) substitution with an alternative substance, and 2) the manufacture of drug substances outside the EU, with the necessary process re-validations and the steps for obtaining market approvals from national and EU health authorities.

In both NUS, the drugs would not be available for the patients until new approvals by authorities were acquired. This could take up to 10 years, even if industry would identify a technically feasible alternative earlier.

SEAC considers that the rationale behind these options and the related timelines for both are clearly presented and described. The two non-use scenarios are considered plausible given the specific market and situation of the applicants (niche drugs manufacturing requiring strict and lengthy market approvals).

What is likely to happen to the use of the substance if an authorisation was not granted?

- The use would cease altogether

What is likely to happen to jobs in the European Union if an authorisation was refused?

- No jobs would be lost in the European Union

Socio-economic impacts of continued use

The first drug produced under the use applied for, Palivizumab, protects babies at risk of respiratory syncytial virus (RSV), which causes severe lower respiratory tract illness. The applicant describes the use and therapeutic value of the drug, e.g. by summarising four cost-effectiveness studies published on the drug. The benefits of Palivizumab relate e.g. to its effectiveness in reducing the risk of hospitalisation caused by RSV infection. According to the application, around 34 million cases of lower respiratory tract infection associated with RSV occur around the world in children under the age of five each year.

The second drug produced under the use applied for, Moxetumomab, is an orphan drug intended for non-chemotherapy cancer treatment. It primarily benefits patients with relapsed or refractory hairy cell leukaemia. According to the applicant, the revenues from marketing orphan drugs like this one just cover or only modestly exceed the costs of development of the

drug. This implies that there will hardly be a competitor offering a similar drug.

According to the applicant, there are currently no alternative pharmaceutical products for either of the medications available from other manufacturers. However, the applicant states that the patent for Palivizumab will expire two years after the sunset date for 4-tert-OPnEO. Following the typical pattern in the pharmaceutical industry, this usually means that generic drugs may enter the market after expiry of the patent. There are already indications that this may also be the case for this drug. Consequently, the company's profits from the sales of this drug are expected to decline over the next decade. The applicants are aware of development efforts by a competitor to develop a new treatment for RSV, which is currently positioned to come to market in 2025 or beyond. However, they do not know if the competitor's treatment under development also requires the use of 4-tert-OPnEO in its manufacturing process. If this was the case, then the new drug would also require an authorisation if produced in the EU. In any case, the competitor would need to obtain a market approval for placing its product on the EU market.

The applicant estimates the costs related to R&D and for obtaining market approval for the changes in the current way of producing the two drugs to be around €14 million for the orphan drug Moxetumomab and €31 million for Palivizumab (NPV for 12 years). These costs are hence avoided if substitution is not required.

The estimated costs of NUS2 (relocation outside EU) are even higher (€50 million for both drugs combined) than those of the substitution scenario. Therefore, in analysing the SEA arguments of the applicant, only the substitution scenario has been considered in more detail.

In comparison, the applicant estimates the complete incineration of 4-tert-OPnEO containing production waste, and thus the elimination of any residual releases to the environment, to be much less costly (the cost is available to SEAC but claimed confidential) and consequently clearly more cost-effective in reducing risk than substitution. SEAC recognises the point made by the applicant even if technical risk management measures to reduce releases are not alternatives to the use of the substance as such.

In conclusion, SEAC can accept the arguments brought forward by the applicants. The applicants supplied information regarding the number of cases of each disease and some general figures regarding economic impacts of treating RSV. However, SEAC regrets that no more detailed information has been brought forward regarding the situation of potential new competitor drugs for RSV. The only information available to SEAC indicates that an RSV drug that has been announced to be market ready after 2025 still depends on the use of OPE in the production process. So the supposed drop in profitability for Palivizumab seems by no means a given. However, based on the currently available information, SEAC has to consider that both drugs are without competition.

5.3. Combined assessment of impacts

The applicants conclude that the risk from granting an authorisation for their use is negligible as both liquid and solid waste is incinerated. The applicant estimates that the cost of eliminating OPE altogether by complete substitution would be about €45 million for both sites combined over the time period considered. This corresponds to €0.8-2.5 million per site per year. This translates to a cost of avoided emissions of more than €80 billion per kg of reduced emission of OPE for Biberach manufacturing site and more than €60 billion per kg of reduced emission of OPE for the Vienna manufacturing site. This is not considered economically justifiable by the applicants if compared with the costs of incineration of waste water with

residual OPE, as proposed in the continued use scenario, resulting in cost figures of around €10 000-50 000 per year per site SEAC accepts this calculation.

5.4. SEAC's view on Socio-economic analysis

SEAC considers that the applicants NUS1 is well justified, primarily because of the required approvals from the health authorities. In addition, the current early state of R&D into alternatives to 4-tert-OPnEO in the purification processes for pharmaceuticals supports the applicants' NUS. SEAC notes that based on the information provided on costs and the time needed for market approval, substitution is not considered a viable option for the applicant.

The applicants did not fully quantify the benefits of continued use to patients. However, they presented some data on effectiveness of Palivizumab and related monetised impacts. They also indicate that since the market approval in 1999, Palivizumab has been used in treatment of more than 3 million patients with RSV. Moreover, currently this drug is the only medical treatment for the prevention of RSV in paediatric patients. Since Moxetumomab pasudotox only received market approval in 2018 and in view of its designation as an "orphan drug", both in the EU and the USA, the number of treated patients so far is less than 150 (less than 100 in the USA and less than 50 in the EU and Canada). Moreover, currently this drug is the only one approved in the USA for third line therapy of Hairy Cell Leukaemia.

SEAC considers that the description the applicants provided on the use and therapeutic values of the two drugs is sufficient to assess and conclude on the societal benefits of continued use. The applicant also estimates the economic impacts of substitution (R&D and market approval costs estimated at €45 million in 12 years) and provides a breakdown of costs on the different activities. SEAC considers that the applicants' calculations are sufficient to assess the direct cost of substitution to the applicants. SEAC notes that the assessment of negative economic impacts to the applicant and AstraZeneca, e.g. in terms of profit losses due to the disruption of the production, would further strengthen the analysis and increase the benefits of continued use.

SEAC considers that cost-effectiveness estimates of €60-80 billion per kg of reduced emission of OPE are appropriately derived based on the estimated direct cost of substitution for the applicant and the release estimates scrutinised by RAC.

SEAC takes note of the conclusion of RAC that the releases (0.015-0.045 g/year) have been minimised to the extent that the likelihood of adverse effects from the use of 4-tert-OPnEO is negligible (i.e. nearing zero). Consequently, SEAC considers that the potential for endocrine disrupting effects in the environment is insignificant.

Table 5: Summary of the main impacts as evaluated by SEAC

Description of the impact	**Magnitude of impacts**
Economic and social impacts of continued use	
Availability of medication to respiratory syncytial virus and for non-chemotherapy cancer treatment	Palivizumab has been used in treatment of more than 3 million patients since 1999. Patients treated with Moxetumobab pasudotox is less than 150 due to recent market approval in 2018.
Avoided costs of R&D and market approval	€45 million (total for 12 years)

Profit losses and unemployment effects are not significant according to the applicants	Not available as considered insignificant by the applicant
Human health and environmental impacts of continued use	
Releases to the environment	0.015-0.045 g/year
Cost of avoiding the remaining releases (cost-effectiveness)	€60-80 billion per kg

5.5. Conclusion on the socio-economic analysis

SEAC has no substantial reservations on the quantitative and qualitative elements of the applicant's assessment of the benefits and the risks to the environment associated with the continued use of the substance. This conclusion is made on the basis of:

- the application for authorisation,
- SEAC's assessment of the benefits of continued use,
- SEAC's assessment of the availability, technical feasibility and economic viability of alternatives,
- any additional information provided by the applicant or its downstream users,
- RAC's assessment of the risks to the environment.

6. Proposed review period

☐ Normal (7 years)

☒ Long (12 years)

☐ Short (…. years)

☐ Other: _____ years

When recommending the review period SEAC took note of the following considerations:

6.1 RAC's advice

RAC gave no advice on the length of the review period.

6.2. Substitution and socio-economic considerations

The applicants request a review period of 12 years. According to the applicants, the cost of reducing releases to the environment by substituting 4-tert-OPnEO will always be more expensive than the use scenario with incineration of the waste will always be more expensive. The applicant estimates that the substitution process itself would take at least 10.5 years for Palivizumab and 5.5 years for Moxetumomab. As already explained above, based on the information provided on costs and the time needed for market approval, substitution is not considered a viable option for the applicants.

AstraZeneca is developing a next generation biologic treatment (MEDI8897) for RSV with a manufacturing process that does not use 4-tert-OPnEO. According to the applicants, the current probability of success for this drug is uncertain but still only between 30 and 40 %. Manufacture of Palivizumab will need to continue until MEDI8897 is commercially available and proven to be successful in the same markets as Palivizumab, in order to meet the needs of all patients taking Palivizumab. The applicants have requested a review period of 12 years to allow for clinical trials and commercialisation of the alternative drug (MEDI8897). If Palivizumab cannot be replaced in all markets by MEDI8897, and no other alternative dug emerges in these markets, then AstraZeneca may test substitutes for 4-tert-OPnEO in the manufacture of Palivizumab (preferably those which were proven effective in the manufacture of new drugs). However, according to the applicants, AstraZeneca does not have the capacity to proceed with MEDI8897 and proceed at the same time with the process of substitution for 4-tert-OPnEO in Palivizumab, and so are focusing resources on bringing the MEDI8897 to market. Regarding Moxetumomab, AstraZeneca has not considered a potential end date for its manufacture and intends to continue to manufacture it for HCL patients using the current process.

SEAC recognises that technically feasible alternatives for the production of Moxetumomab could become available to the applicant already over a 7-year review period if the applicant and AstraZeneca allocated the necessary resources to substitution. However, costs related to R&D and for obtaining market approvals are high. SEAC agrees that substitution would require large investments and therefore concludes that it is very likely that suitable (economically feasible) alternatives will not become available over the next decade. SEAC notes also that the applicants have minimised releases and the related negative environmental impacts are insignificant.

Taking into account these points, SEAC recommends a 12-year review period.

7. Proposed additional conditions for the authorisation

Were additional conditions[17] proposed for the authorisation?

☐ Yes

☒ No

7.1 Description

RAC

Proposed additional conditions

None

SEAC

Proposed additional conditions

None

[17] Conditions are to be proposed where RCR is > 1, OCs and RMMs are not appropriate and effective, risk is not adequately controlled, minimisation of emissions is not demonstrated.

7.2. Justification

RAC is of view that:

- the applicants have demonstrated that releases to environmental compartments have been prevented or minimised as far as technically and practically possible based on the OCs & RMMs in the ES;
- the release estimates provided by the applicants are appropriate; and
- may result in up to approximately 45 mg per year emissions of 4-tert-OPnEO to the environment. Risks to the environment cannot be excluded for non-threshold substances even at low exposure levels. However, in this case, RAC is of the view that the likelihood of adverse effects is negligible (i.e. nearing zero).

8. Proposed monitoring arrangements for the authorisation

Were monitoring arrangements[18] proposed for the authorisation?

☐ Yes

☒ No

8.1 Description

None

8.2 Justification

As in section 7.

9. Recommendations for the review report

Were recommendations for the review report made?

☐ Yes

☒ No

9.1 Description

None

9.2 Justifications

As in section 7.

[18] Monitoring arrangements for the authorisation are to be proposed where RCR is < 1, OCs and RMMs are appropriate and effective, risk is adequately controlled, minimisation of emissions is demonstrated – but there are some moderate concerns.

10. Comments on the draft final opinion

Did the applicant(s) provide comments on the draft final opinion?

☒ Yes

☐ No

Comments of the applicant(s)

Was action taken resulting from the analysis of the comments of the applicant(s)?

☒ Yes

☐ No

☐ Not applicable – the applicant(s) did not comment

Reasons for introducing the changes and changes made to the opinion

The applicants provided reasons for not submitting a substitution plan, stressed that at present there is no evidence that suitable alternatives in general to 4-tert-OPnEO are available to its use for the manufacture of both APIs, and requested that the opinion would clarify further why the risk reduction evaluation is “not applicable”. Sections 4.2 and 4.4 were amended to reflect the comments from the applicants on the draft opinion.

Reasons for not amending the opinion

Not applicable.