Biocidal Products Committee (BPC)

Opinion on the application for renewal of the approval of the active substance:

medetomidine

Product type: 21

ECHA/BPC/422/2024

Adopted

28 May 2024

Opinion of the Biocidal Products Committee

on the application for renewal of the approval of the active substance medetomidine for product type 21

In accordance with Article 14(3) of Regulation (EU) No 528/2012 of the European Parliament and of the Council 22 May 2012 concerning the making available on the market and use of biocidal products (BPR), the Biocidal Products Committee (BPC) has adopted this opinion on the application for renewal of the approval in product type 21 of the following active substance:

Common name:	**medetomidine**
Chemical name:	**(RS)-4-[1-(2,3-dimethylphenyl)ethyl]-1H-imidazole**
EC No.:	**N/A**
CAS No.:	**86347-14-0**
New active substance	

This document presents the opinion adopted by the BPC, having regard to the conclusions of the evaluating Competent Authority. The assessment report, as a supporting document to the opinion, contains the detailed grounds for the opinion.

Process for the adoption of the BPC opinion

Following the submission of an application by I-Tech AB on 27 June 2021, the evaluating Competent Authority Norway submitted an assessment report and the conclusions of its evaluation to the Agency on 18 August 2023, after performing a full evaluation of the renewal application. In order to review the renewal assessment report and the conclusions of the evaluating Competent Authority, the Agency organised consultations via the BPC (BPC-51) and its Working Groups (WG-I-2024). Revisions agreed upon were presented and the assessment report and the conclusions were amended accordingly.

Information on the fulfilment of the conditions for considering the active substance as a candidate for substitution was made publicly available at *https://echa.europa.eu/potential-candidates-for-substitution-previous-consultations/-/substance-rev/74905/term* on 3 November 2023, in accordance with the requirements of Article 10(3) of Regulation (EU) No 528/2012. Interested third parties were invited to submit relevant information by 4 January 2024.

Adoption of the BPC opinion

Rapporteur: Norway

The BPC opinion on the application for renewal of the active substance medetomidine in product type 21 was adopted on 28 May 2024 .

The BPC opinion takes into account the comments of interested third parties provided in accordance with Article 10(3) of BPR.

The BPC opinion was adopted by consensus. The opinion is published on the ECHA webpage.

Detailed BPC opinion and background

1. Overall conclusion

Since medetomidine fulfils the criteria set in Article 5(1)(d) of the BPR, the overall conclusion of the BPC is that the approval of medetomidine in product type 21 should not be renewed, unless one of the conditions for derogation in Article 5(2) of the BPR is met. The detailed grounds for the overall conclusion are described in the renewal assessment report.

2. BPC Opinion

2.1. BPC Conclusions of the evaluation

a) Presentation of the active substance including the classification and labelling of the active substance

Medetomidine is a synthetic compound used as a surgical anaesthetic and analgesic in veterinary medicine and as a sedative in human medicine. The substance is manufactured as a racemic mixture of two stereoisomers: dexmedetomidine and levomedetomidine. Only dexmedetomidine is demonstrated to have sufficient biocidal activity when medetomidine is used as an antifouling substance. Dexmedetomidine is a highly selective α2 adrenoceptor agonist on presynaptic neurons. The stimulation of these receptors leads to a decrease in norepinephrine release from presynaptic neurons with inhibition of postsynaptic activation, which attenuates CNS (Central Nervous System) excitation, especially in the locus coeruleus of the brain. The pharmacological sedative effect of medetomidine is also its main toxicological effect. A similar mode of action (activation of specific neuro-receptors in shell-building organisms leading to an anti-settling effect) is the basis of its biocidal activity as an antifouling agent.

The evaluation as basis of this opinion covers the use of medetomidine in product-type 21 (antifouling products). Medetomidine acts by binding to octopamine receptors on the larval surface of marine organisms, such as acorn barnacles, stalked barnacles and tubeworms. This results in increased motility, which inhibits the settling behaviour of the larvae.

Specification for the reference source was not established in the first approval and the reference specification of medetomidine was instead established for the renewal. The reference specification includes one source. The physico-chemical properties and physical hazards of the active substance have been evaluated and are deemed acceptable for the appropriate use, storage, and transport of the active substance. Validated analytical methods are available for the relevant matrices water, soil, air, animal and human body fluids and tissues and residues in food and feedstuffs.

The following information was generated since the initial approval and was submitted by the applicant:

I. The human exposure assessment was re-calculated according to recommendation No 17 of the BPC Ad hoc Working Group on Human Exposure, agreed at the Human Health Working Group I-2020 on 25 March 2020.

II. A new human intravenous injection study on toxicokinetic was provided. The study did not affect the outcome of the risk assessment (Scheinin 2017).

III. Endocrine disruptor (ED) assessment of medetomidine has been included. There were relevant data from the literature and/or regulatory studies available.

IV. Analytical profile of five representative batches of medetomidine.

V. Field study report and efficacy data on the enantiomer levomedetomidine.

VI. A scientific study on photochemical fate was provided. The study did not affect the outcome of the risk assessment (Cai et al. 2021).

VII. A new laboratory study on the aerobic transformation in marine aquatic sediment systems was provided (OECD 308, Ogston 2022).

VIII. A new laboratory study on the bioaccumulation in Oyster (*C. virginica*) was provided to support new regulatory requirements (OCSPP 850.1710, Garcia et al., 2021).

IX. In total five studies were provided that were generated for other regulatory regions and do not impact key endpoints or alter the conclusion in the risk assessment compared to the previous approval. These studies have not been evaluated by the eCA. The studies are acute toxicity to sheepshead minnow (850.1075, Maunder 2012a), Acute toxicity to *Amercamysis bahia* (OPPTS 850.1035, Fournier 2013), effects on the aquatic plant *Lemna gibba* (OCSPP 850.4400, Softscheck 2012), effects on non-target plants (OCSPP 850.4100, Martin 2013), and acute oral toxicity to northern bobwhite (OCSPP 850.2100, Stafford 2012).

The current classification and labelling for **medetomidine** according to Regulation (EC) No 1272/2008 (CLP Regulation):

Classification according to the CLP Regulation	
Hazard Class and Category Codes	Acute Tox. 2 Acute Tox. 2 STOT SE 1 STOT SE 3 STOT RE 1 Aquatic Acute 1 Aquatic Chronic 1
Labelling	
Pictogram codes	GHS08 GHS06 GHS09
Signal Word	Danger
Hazard Statement Codes	H300 H330 H370 H336 H372 H410
Specific Concentration limits, M-Factors	Aquatic acute M=1 Aquatic chronic M=100
Justification for the proposal	
-	

b) Intended use, target species and effectiveness

The field of use envisaged and function and organisms to be controlled are as follows:

Main group 4 (MG04) – Other biocidal products

Product-type 21 (PT21) – Antifouling products

Anti-fouling products containing medetomidine are to be used on hulls of vessels such as commercial and government ships, super-yachts and pleasure crafts, to surfaces such as outdrives, outboard legs, propellers and stern gears of pleasure crafts, and to structures and objects subject to immersion. This is to protect submerged surfaces from fouling by hard fouling (shell-building) marine organisms, such as acorn worms and stalked barnacles and tube-building polychaetes such as marine tubeworms. All surfaces are treated while they are out of the water. Application will be by professional users via airless spray, brush or roller in paint and by non-professionals via brush or roller in paint and by spray application via paint in an aerosol can.

The data on medetomidine and the representative biocidal product has demonstrated sufficient efficacy against the target species. Since medetomidine acts as a non-lethal deterrent on target organisms and its effect is reversible, resistance development is less likely to occur.

c) Overall conclusion of the evaluation including need for risk management measures

Human health

The most prominent effect of the hazard profile of medetomidine in both animals and humans is the induction of sedation. This is an acute effect observed in both single and repeat dose studies. In humans, the lowest and most robust NOAEL (0.4 µg/kg bw) for this effect was identified from an intravenous (i.v.) study. In animals, the lowest NOAEL (6 µg/kg bw/day) for the effect was identified in an i.v. rabbit developmental toxicity study. The animal data support the human data. The human NOAEL for sedation was used to derive the short-term, medium-term and long-term AELs.

Medetomidine is not mutagenic, carcinogenic or a reproductive toxicant.

It was agreed, that based on the overall WoE medetomidine has endocrine disrupting properties with respect to humans. Medetomidine shows adverse effects on the steroidogenesis and non-EATS modalities in regulatory studies, and in human and animal studies from open literature. The ED activity is demonstrated by inhibition of steroidogenesis and aromatase in *in vitro* studies, and the knowledge of the activity of α2-adrenoceptor agonism which is well described in open literature for the substance. The biological plausibility is well supported by toxicological and pharmacological literature. As a surgical anaesthetic and analgesic medicine, the substance has been specifically designed to bind and activate the α2-adrenergic receptor which is an integral part of the sympathoadrenal system. This agonism leads to attenuation of neuroendocrine responses to stress. Although no harmonized test methods and assessment frameworks for non-EATS endpoints are currently available, medetomidine is considered to have endocrine disrupting properties according to Section A of Regulation (EU) 2017/2100.

The table below summarises the human health exposure scenarios assessed.

Summary table: human health scenarios			
Scenario	**Primary or secondary exposure and description of scenario**	**Exposed group**	**Conclusion**
Airless spraying application	Primary exposure Airless spraying application by sprayman	Professional	No conclusion possible
Mixing/loading	Primary exposure Potman mixing and loading paint into reservoirs for airless spraying in dockyards and on slipways	Professional	No conclusion possible
Cleaning of spray equipment	Primary exposure Cleaning of spray equipment Sprayman or potman	Professional	No conclusion possible
Brush and roller application	Primary exposure Professional users who apply antifoulants to boats on a small scale	Professional	No conclusion possible
Airless spraying application	Primary exposure Cleaning a brush used for solvent-based formulations	Professional	No conclusion possible
Mixing/loading	Primary exposure Paint removal by sand blasting	Professional	No conclusion possible
Cleaning of spray equipment	Primary exposure Grit Filler fills the sand blasting machine with a ratio of water and grit using either new grit from paper bags or used grit (recycled during the task) that may be contaminated.	Professional	No conclusion possible
Brush and roller application	Primary exposure Non-professional users who apply antifoulants to boats direct from can or paint tray	Non-professional	No conclusion possible
Spray operations using an aerosol can	Primary exposure Application using a pre-pressurised aerosol can to small areas of pleasure crafts and areas that are difficult to access using a brush or roller. This includes stern drives, sail drives and propellers with drive attachments.	Non-professional	No conclusion possible
Cleaning of brush and roller	Primary exposure Cleaning a brush used for solvent-based formulations	Non-professional	No conclusion possible
Paint removal	Primary exposure High pressure water washing (HPW), hydro-blasting, abrasion (rubbing with a wire brush) and abrasive blasting using dry grit or wet slurry.	Non-professional	No conclusion possible
Cleaning work clothing at home	Secondary exposure Cleaning work clothing at home	Non-professional	No conclusion possible
Accidental exposure	Secondary exposure Young child touching a boat surface	Bystander	No conclusion possible

A conventional human health exposure assessment (excluding ED properties) was undertaken for systemic effects following exposures via the inhalation and dermal routes for professional and non-professional use. The exposure calculation for this scenario does not comply with current standards but is accepted since re-assessment would not have an impact on the overall outcome of the renewal assessment.

With regard to endocrine disrupting properties, no agreed methodology is available on how to perform a risk assessment for endocrine disruptors under the BPR. Moreover, due to the limitation of data in regard to sensitive groups, it is not possible to identify the absolute threshold which could be used to protect the whole population. Thus, it is not possible to establish a quantifiable threshold that would give confidence in a conclusion on safe use. Without considering that medetomidine has endocrine-disrupting properties, the risk assessment performed using the conventional methodology showed no unacceptable risks for medetomidine for humans, except for dermal and hand-to-mouth exposure for a young child touching wet paint on a boat surface freshly treated with medetomidine in the representative product.

Regarding the overall acceptability of the risk to human health, no conclusion is possible.

Environment

Medetomidine is very persistent in sediment, and available evidence indicates that medetomidine is considered toxic to the environment, but it does not bioaccumulate. Medetomidine is therefore considered a candidate of substitution because it meets at least two of the criteria for being PBT.

There is sufficient evidence that medetomidine disrupts the S- and non-EATS modalities and that in the absence of evidence demonstrating that these effects are not relevant at the population level, these effects should be considered as adverse for mammals as non-target organisms (NTOs). Medetomidine is considered to have population relevant endocrine disrupting properties to mammals as NTOs affecting endpoints which can impair the ability to cope with additional stress. The conclusion is supported by the same knowledge from open literature as for human health.

For the initial approval of medetomidine, the environmental exposure assessment was based on concentrations in the area adjacent to the marina/harbour. For the first approval of PT21 active substances, an agreement was made for Annex I listing purposes that acceptable risk in the wider environment (as defined by the areas adjacent to the marina and harbour scenario) was sufficient in cases where an unacceptable risk was identified within the marina/harbour. No re-evaluation of the assessment as conducted for the first approval of medetomidine took place, since a re-evaluation would not have an impact on the overall outcome of the renewal assessment.

The table below summarises the exposure scenarios assessed.

Summary table: environment scenarios			
Scenario	**Description of scenarios including environmental compartments**		**Conclusion**
	Commercial ships	**Pleasure craft**	
In-service life stage	OECD-EU Commercial harbour OECD-EU Shipping lane	OECD-EU Marina	No conclusion possible

In a conventional risk assessment (excluding ED properties), comparing the predicted exposure concentration (PEC) with the predicted no effect concentration (PNEC) no unacceptable risks are calculated for the commercial ship scenarios. For the pleasure craft scenario, unacceptable risks were identified within the marina, while for the areas adjacent to the marina, PEC/PNEC values were below the threshold value of 1.

Currently no thresholds/safe concentration limits with regard to environmental NTOs can be derived for the endocrine disrupting properties of medetomidine due to a variety of uncertainties associated with such an approach. In practice, the lack of threshold concentrations means that a quantitative risk assessment with respect to ED properties cannot be conducted. Thus, it is not possible to conclude on the risk derived from the ED properties.

Regarding the overall acceptability of the risk to the environment, no conclusion is possible due to the non-conclusion of the risk regarding ED and NTOs.

Overall conclusion

Medetomidine is considered to have endocrine disrupting properties with respect to humans and non-target organisms. No conclusion on the level of risks of using medetomidine considering its endocrine disrupting properties can currently be drawn, as neither guidance nor a harmonised understanding on the principles of an ED risk assessment is available.

2.2. Exclusion, substitution and POP criteria

2.2.1. Exclusion and substitution criteria

The table below summarises the relevant information with respect to the assessment of exclusion and substitution criteria:

Property		**Conclusions**	
CMR properties	Carcinogenicity (C)	No classification required	Medetomidine does not fulfil criterion (a), (b) and (c) of Article 5(1)
	Mutagenicity (M)	No classification required	
	Toxic for reproduction (R)	No classification required	
PBT and vPvB properties	Persistent (P) or very Persistent (vP)	vP	Medetomidine does not fulfil criterion (e) of Article 5(1) but fulfils criterion (d) of Article 10(1)
	Bioaccumulative (B) or very Bioaccumulative (vB)	not B or vB	
	Toxic (T)	T	
Endocrine disrupting properties	Section A of Regulation (EU) 2017/2100: ED properties with respect to humans	Yes	Medetomidine fulfils Article 5(1)(d) and Article 10(1)(e)

Property		Conclusions	
	Section B of Regulation (EU) 2017/2100: ED properties with respect to non-target organisms	Yes	
	Article 57(f) and 59(1) of REACH	No	
	Intended mode of action that consists of controlling target organisms via their endocrine system(s)	No	
Respiratory sensitisation properties	No classification required		
Concerns linked to critical effects other than those related to endocrine disrupting properties	No other concerns identified		
Proportion of non-active isomers or impurities	Medetomidine is a racemic active substance made up of 49.75 % dexmedetomidine (the active component) and 49.75 % levo edetomidine (non-effective component). Given this, medetomidine does fulfil this criterion.		

Consequently, the following is concluded:

Medetomidine does meet the exclusion criteria laid down in Article 5(1)(d) of the BPR.

Medetomidine does meet the conditions laid down in Article 10 of the BPR and is therefore considered as a candidate for substitution. Medetomidine is considered a candidate for substitution in accordance with Article 10(1)(a), (d), (e) and (f) of the BPR because the substance meets at least one of the exclusion criteria in Article 5(1) of the BPR as listed above, it meets at least two of the criteria for being PBT, and it contains a significant proportion of non-active isomers.

The exclusion and substitution criteria were assessed in line with the "Note on the principles for taking decisions on the approval of active substances under the BPR", "Further guidance on the application of the substitution criteria set out under article 10(1) of the BPR" and "Implementation of scientific criteria to determine the endocrine –disrupting properties of active substances currently under assessment" agreed at the 54th, 58th and 77th meeting respectively, of the representatives of Member States Competent Authorities for the implementation of Regulation (EU) No 528/2012 concerning the making available on the market and use of biocidal products. This implies that the assessment of the exclusion criteria is based on Article 5(1) of the BPR and the assessment of substitution criteria is based on Article 10(1)(a), (b), (d), (e) and (f) of the BPR.

2.2.2. POP criteria

Medetomidine fulfils the criteria for being vP and T. However, medetomidine does not demonstrate the potential for long range transport. In view of this, medetomidine does not meet the criteria for being a persistent organic pollutant.

2.2.3. Identification of potential alternatives substances or technologies, including the results of the public consultation for potential candidates for substitution

As the conditions of Article 10(1)(a), (d), (e) and (f) of the BPR are met for medetomidine, a consultation on potential candidates for substitution was held between 3 November 2023 and 4 January 2024. One comment from the applicant was received.

According to the submitted comment from the applicant, there are no suitable alternatives to medetomidine in PT 21 as technology for protection against barnacle fouling when considering impacts of increased greenhouse gas emissions and the transfer of invasive species. According to the applicant, the degradation profiles of the biocidal alternatives are slightly better than medetomidine when considering current classifications, however, when considering actual environmental fate, the substances have more similar properties, i.e., copper compounds do not degrade in the environment and tralopyril could form a metabolite classified as very persistent. Thus, the applicant argues that substitution is not guaranteed to offer a benefit to human health or the environment. According to the applicant, the hazards for humans and the environment varies between the non-chemical alternatives, but they all pose a risk of contributing to transport of invasive species in the marine environment. The increased emissions from commercial vessels with poor fouling protection have not been taken into consideration, but it is a significant factor to have in mind when deciding on suitable alternatives for fouling prevention.

The Analysis of alternatives (AoA) annexed to this Opinion comes to a different outcome. The AoA identifies 26 potential alternative substances or technologies. The intended use of medetomidine has been divided into use on commercial vessels and use on pleasure crafts. There are 12 biocidal active substances in PT 21 (in addition to medetomidine) in ECHA's database of active substances. The eCA concludes that the following eight PT 21 active substances are suitable alternatives to medetomidine: DCOIT, copper pyrithione, copper flakes, copper thiocyanate, dicopper oxide, tolylfluanid, dichlofluanid, and tralopyril. These alternatives have a less hazardous toxicological profile than medetomidine based on the fact that these do not fulfil the exclusion criteria, but also based on a comparison of human health reference values and classification. All of the alternative active substances have intended uses that are similar to medetomidine and in addition all of the alternative active substances have a wider usage than medetomidine since they are effective against a broader range of fouling organisms. These eight alternative active substances are safer than medetomidine in that they have a less hazardous toxicological profile than medetomidine. The alternatives are technically and economically feasible and are available from the perspective of production capacities.

In addition to biocidal active substances, several non-biocidal alternatives have been identified. Some of these are ultrasonic systems, hydrophobic coatings, UV light, air lubrication technology, in-water cleaning, silicon-based coatings, and non-biocidal hard coatings. In total, 14 potential non-biocidal alternatives were identified as alternatives to medetomidine in PT 21. Out of these, three technologies are considered as alternatives for commercial vessels: non-biocidal hard coatings, silicon-based coatings and in-water (proactive) cleaning. For pleasure crafts, six technologies are considered as alternatives to medetomidine: non-biocidal hard coating, silicon-based coatings, ultrasonic systems, antifouling films/wraps, in water reactive cleaning, and in-water proactive cleaning.

These non-biocidal alternatives are safer alternatives in that they have a lower overall risk profile compared to medetomidine. The alternatives are also generally available on the EU market. Furthermore, the alternatives are considered technical and economic feasible although they may not cover the full spectrum of the intended uses. This outcome does not mean that the alternatives should be disregarded as suitable alternatives but rather considered as an integral part of fouling protection.

Overall, the eCA has identified a total of 11 suitable alternative substances or technologies for the use on commercial vessels and 14 suitable alternative substances or technologies for the use on pleasure crafts.

2.3. BPC opinion on the application for renewal of the active substance medetomidine in product type PT 21

As the exclusion criteria are met, medetomidine should not be approved unless one of the conditions for derogation set in Article 5(2) of the BPR is met.

In view of the conclusions of the evaluation, it is proposed that medetomidine shall not be renewed under the BPR as an active substance in antifouling products (product-type 21). Medetomidine fulfils the exclusion criteria as an endocrine disruptor for human health, it is an endocrine disruptor for the environment, and also meets two of the criteria for being PBT, vP and T. There are both alternative technologies and a range of alternative active substances with a less hazardous toxicological profile than medetomidine.

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