Biocidal Products Committee (BPC)

Opinion on the application for approval of the active substance:

medetomidine

Product type: 21

ECHA/BPC/38/2015

Adopted

3 February 2015

Annankatu 18, P.O. Box 400, FI-00121 Helsinki, Finland | Tel. +358 9 686180 | Fax +358 9 68618210 | echa.europa.eu

Opinion of the Biocidal Products Committee

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

In accordance with Article 90(2) 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 approval in product type 21 of the following active substance:

Common name:	**medetomidine**
Chemical name(s):	**(RS)-4-[1-(2,3-dimethylphenyl)ethyl]-1H-imidazole**
EC No.:	**not available**
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 BPC opinions

Following the submission of an application by I-Tech AB on 27/04/2009, the evaluating Competent Authority UK submitted an assessment report and the conclusions of its evaluation to the Agency on 12 March 2014. In order to review the assessment report and the conclusions of the evaluating Competent Authority, the Agency organised consultations via the BPC and its Working Groups. 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 http://echa.europa.eu/en/addressing-chemicals-of-concern/biocidal-products-regulation/public-consultation-on-potential-candidates-for-substitution on 16 June 2014, 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 15 August 2014.

Adoption of the BPC opinion

Rapporteur: BPC member for United Kingdom

The BPC opinion on the approval of the active substance medetomidine in product type 21 was adopted on 3 February 2015. The BPC opinion takes into account the comments of interested third parties provided in accordance with Article 10(3) of Regulation (EU) No 528/2012.

The BPC opinion was adopted by consensus.

Detailed BPC opinion and background

1. Overall conclusion

The overall conclusion of the BPC is that the medetomidine in product type 21 may be approved. The detailed grounds for the overall conclusion are described in the 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 both a surgical anaesthetic and analgesic in veterinary medicine and sedative in human medicine. 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.

This evaluation 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. The effect is reversible and can occur on exposure to medetomidine. At higher concentrations medetomidine, in addition to the anti-settling effect, can also cause larval mortality. Specifications for the reference source are established. The specifications of the reference source are covered by the batches used in toxicology and ecotoxicology studies.

The physico-chemical properties of the active substance and biocidal products have been evaluated and are deemed acceptable for the appropriate use, storage and transportation of the active substance and biocidal products. Validated analytical methods are available for the analysis of medetomidine as manufactured and for the determination of impurities. Further validation data are required for the analytical methods in plasma (medetomidine) and sediment (residues). An analytical method for the analysis of medetomidine in air is required. An analytical method in soil is not required as it had been agreed that the analytical method in sediment would be acceptable due to the similarity of the matrices soil and sediment. Please refer to Section 2.5 and to the Asessement Report for details.

There is currently no harmonised classification of the active substance medetomidine according to Regulation (EC) No 1272/2008 (CLP Regulation). This active substance is included in the Rapporteur Member State's harmonised classification work programme and will be progressed as soon as is possible.

The proposed classification and labelling by the evaluating Competent Authority of the active substance medetomidine according to Regulation (EC) No 1272/2008 (CLP Regulation) is:

Classification according to the CLP Regulation	
Hazard Class and Category Codes	Acute Tox 2 (H300, H330) STOT-SE 3 (H336) Acute Aquatic 1 (H400) Aquatic Chronic 1 (H410)
Labelling	
Pictograms	GHS06 GHS09
Signal Word	DANGER
Hazard Statement Codes	H300: Fatal if swallowed. H330: Fatal if inhaled. H336: May cause drowsiness or dizziness H400: Very toxic to aquatic life H410: Very toxic to aquatic life with long lasting effects
Specific Concentration limits, M-Factors	Acute, M = 1 Chronic, M = 100 (non-rapidly degradable)

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 craft, to surfaces such as outdrives, outboard legs, propellers and stern gears of pleasure craft, 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 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 assessment of the biocidal activity of the active substance demonstrates that it has a sufficient level of efficacy against the target organisms and the evaluation of the summary data provided in support of the efficacy of the accompanying products establishes that the products may be expected to be efficacious.

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

The overall conclusion from the evaluation of medetomidine for use in product type 21 (antifouling products) is, that it may be possible for Member States to issue authorisations of products containing medetomidine in accordance with the conditions laid down in Regulation (EU) No 528/2012.

It should be noted that assessments carried out for human health and the environment for the limited number of substances under product type 21 (antifouling products) often

indicate unacceptable risks to certain end users and/or environmental compartments exposed to these substances. These assessments also indicate the need for risk mitigation measures, such as technical controls and/or personal protective equipment (PPE), in order to protect end-users using these substances and minimise exposure of the relevant environmental compartments.

It was agreed at the 55th meeting of the representatives of Member State Competent Authorities for the implementation of the BPR to utilise generic conditions in approval regulations (as outlined in section 2.3 below) for all product type 21 substances evaluated as part of the EU Review Programme for existing active substances to reduce the risks for human health and for the environment from use of these substances[1].

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 as the toxicological profile of medetomidine is driven by acute systemic effects, with no specific target organs of toxicity being identified at lower dose levels following repeated exposure.

The table below summarises the exposure scenarios assessed (where relevant these individual scenarios were also in combination as appropriate):

Summary table: human health scenarios		
Scenario	**Primary or secondary exposure and description of scenario, exposed group**	**Acceptable or unacceptable**
Mixing/loading	**Primary exposure:** mixing and loading antifouling product into reservoirs for airless spraying, professionals (potman)	Acceptable with gloves, impermeable coveralls 4% penetration and RPE protection factor 40
Spray application	**Primary exposure:** spray application of antifouling product via airless sprayer, professionals (sprayman)	Acceptable with gloves, double coverall 1% penetration and RPE protection factor 40
Spray application (aerosol can)	**Primary exposure:** spray application of antifouling product via aerosol can, non-professionals	Acceptable
Application by brush/roller	**Primary exposure:** application of antifouling product by brush and roller, professionals (including chandler) and non-professionals	For professionals, acceptable with gloves and impermeable coveralls 4% penetration. For non-

[1] See document: Antifouling (PT21); the way forward for the management of active substances and the authorisation of biocidal products. (CA-March14-Doc.4.2 - Final).

		professionals, acceptable with gloves, clothing penetration factor 50% and a exposure duration of 90 min.
Cleaning of spray equipment	**Primary exposure:** cleaning of spray equipment used to apply antifouling product, professionals	Acceptable.
Cleaning of brushes/rollers	**Primary exposure:** cleaning of brushes/rollers used to apply antifouling product, professionals and non-professionals	Acceptable for professionals and non-professionals.
Grit filling	**Primary exposure:** filling (with sand or grit) of abrasive blasting equipment used for removal of antifouling product, professionals (grit filler)	Acceptable with gloves, double coveralls 1% penetration and RPE protection factor 40
Paint removal (blasting)	**Primary exposure:** removal of antifouling product by abrasive blasting, professionals	Acceptable with gloves, coveralls and RPE protection factor 40
Paint removal (washing of abrasion)	**Primary exposure:** removal of antifouling product by high-pressure water washing or abrasion (rubbing with a wire brush), non-professionals	Acceptable
Cleaning of work clothes	**Secondary exposure:** cleaning of work clothes contaminated from aerosol spray, brush and roller application, non-professional	Acceptable
Young child touching freshly-painted (wet product) surface of treated boat	**Secondary exposure:** Young child touching a boat surface treated with antifouling product when still wet, general public	Unacceptable
Young child touching dry surface of treated boat	**Secondary exposure:** Young child touching a boat surface treated with antifouling product when dry, general public.	Acceptable
Dietary exposure from residues in fish and shellfish	**Secondary exposure:** Consumption of fish and shellfish containing residues of antifouling product, general public	Acceptable.

A quantitative risk assessment was undertaken for systemic effects following exposures via the inhalation and dermal routes. The overall conclusions of the risk characterisation for systemic effects are based on the predicted total systemic body burden. All of the scenarios identified represent medium-term exposure for professional use and short-term exposure for non-professional use.

Professionals

The human health risk assessment identified acceptable risks following primary exposure

of professionals to medetomidine in the representative product provided appropriate personal protective equipment (PPE) (including respiratory protective equipment (RPE) for certain tasks) is worn.

No secondary exposure of professionals to medetomidine is predicted to occur.

Acceptable risks from combined exposure to medetomidine in the representative product were identified for a professional operator spraying and cleaning out the spraying equipment on the same day; and for a professional operator mixing and loading the representative product and cleaning out the spraying equipment on the same day provided appropriate PPE is worn (this includes gloves, coveralls (double coveralls for spraying) and RPE protection factor 40).

Acceptable risks from combined exposure to medetomidine in the representative product were identified for a professional operator applying the representative product by brush and roller and cleaning out the paint brush/roller on the same day provided appropriate PPE is worn (this includes gloves and coveralls).

Non-professionals

Acceptable risks were identified for non-professionals applying medetomidine in the representative product by brush and roller when long-sleeved shirt, long trousers, sturdy foot-wear (clothing penetration value of 50 %) and working gloves are worn.
Acceptable risks were identified for aerosol can spraying at Tier I (where no PPE are needed and a default clothing penetration value of 100 % is used).

An acceptable risk was identified for an adult washing clothes contaminated with medetomidine following use of the representative product.

An unacceptable risk is identified (from 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. However, an acceptable risk is identified for a young child touching dry paint (both dermal and hand-to-mouth exposure) from a boat surface treated with medetomidine in the representative product. Therefore, it is considered that this potential risk to children can be mitigated by suitable labelling of products containing medetomidine intended for non-professional use indicating that unprotected persons should be kept away from treated surfaces until they are dry.

An acceptable risk from combined exposure to medetomidine in the representative product is identified for a non-professional operator applying the representative product by brush and roller and cleaning out the paint brush/roller on the same day provided gloves are worn during the application phase.

Dietary Risk Assessment

A preliminary dietary risk assessment showed that use of medetomidine in the representative product does not pose an unacceptable risk to the consumer as a residue in fish and shellfish.

Environment

The table below summarises the exposure scenarios assessed (where relevant, simultaneous multiple exposure was also assessed):

Summary table: environment scenarios		
Scenario	**Description of scenarios including environmental compartments**	
	Commercial ships	**Pleasure craft**
New building – application	Direct releases to marine surface water following application by spray and brush and roller by professionals	Direct releases to soil and/or Sewage Treatment Plant (STP) following spray, brush and roller application by professionals. Indirect releases to marine surface water via STP by professionals.
Maintenance and repair – application and removal of paint	Direct release to marine surface water following spray application and high pressure washing by professionals	Direct releases to soil (ground water) and/or STP following spray, brush and roller application by professionals; and aerosol spray can and brush and roller application by non-professionals. Direct releases to marine surface water by removal of paint by professionals and non-professionals. Indirect releases to marine surface water via STP by professionals and non-professionals.
In-service life stage	OECD-EU Commercial harbour OECD-EU Shipping lane	OECD-EU Marina
Aggregated exposure	Application and in-service releases were summed up. Removal and in-service releases were summed up.	Removal and in-service releases were summed up
For all scenarios evaluated the exposure is estimated within the harbour or marina as well as adjacent to the harbour and marina (defined as the wider environment). In addition, both for commercial and pleasure craft scenarios, worst case and typical case situations were evaluated.		

Professionals

Acceptable risks were identified for all environmental exposure scenarios following use of medetomidine in the representative product by professionals.

Non-professionals

An unacceptable risk to soil was identified following use of medetomidine in the representative product. Risk mitigation measures (such as advising users to protect the soil during application and removal) are necessary to prevent release of medetomidine to soil.

All other environmental exposure scenarios identified acceptable risks following use of medetomidine in the representative product by non-professionals.

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
	Mutagenicity (M)	No classification required
	Toxic for reproduction (R)	No classification required
PBT and vPvB properties	Persistent (P) or very Persistent (vP)	vP
	Bioaccumulative (B) or very Bioaccumulative (vB)	Not B and not vB
	Toxic (T)	T
Endocrine disrupting properties	The active substance is not considered to have endocrine disrupting properties	
Respiratory sensitisation properties	No classification required	
Concerns linked to critical effects	The potential toxic effect upon children who might touch a freshly painted surface is of concern. However, the mitigation measure indicated (keeping children away from freshly painted surfaces) is not a very restrictive risk management measure. Given this, medetomidine does not fulfil this criterion.	
Proportion of non-active isomers or impurities	Medetomidine is put on the market as a racemic active substance; it is made up of 49.75 % dexmedetomidine (the active component) and 49.75 % levomedetomidine (non-effective component). Given this, medetomidine does fulfil this criterion.	

Consequently, the following is concluded:

Medetomidine does not meet the exclusion criteria laid down in Article 5 of Regulation (EU) No 528/2012.

Medetomidine does meet the conditions laid down in Article 10(1)(d) and 10(1)(f)[2] of Regulation (EU) No 528/2012. Medetomidine is therefore considered as a candidate for substitution by fulfilling two of the criteria for being PBT and by virtue of the fact that it contains a significant proportion of non-active isomers or impurities.

[2] Please note that the public consultation undertaken did not highlight that medetomidine met the conditions laid down in Article 10(1)(f), only Article 10(1)(d).

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" [3] and in line with "Further guidance on the application of the substitution criteria set out under article 10(1) of the BPR"[4] agreed at the 54th and 58th meeting respectively, of the representatives of Member States Competent Authorities for the implementation of Regulation 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) and the assessment of substitution criteria is based on Article 10(1)(a, b, d, e and f).

During public consultation a non-confidential comment was received from third parties. The non-confidential comment included information claiming the specific characteristics of the substance, being a new active substance, with a reversible effect, and describes the position of the submitter regarding fulfilment of the substitution criteria (P and T). In addition, there are several other active substances intended for use in the same product type already approved or are currently being reviewed under Regulation (EU) No 528/2012.

2.2.2. POP criteria

Medetomidine fulfils the criteria for being P 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.

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

In view of the conclusions of the evaluation, it is proposed that medetomidine shall be approved and be included in the Union list of approved active substances, subject to the following specific conditions:

1. Specification: minimum purity of the active substance evaluated: 99.5 % w/w. Medetomidine is manufactured as a racemic mixture of R and S enantiomers: dexmedetomidine and levomedetomidine.

2. Medetomidine is considered a candidate for substitution in accordance with Article 10(1) (d) and 10(1) (f) of Regulation (EU) No 528/2012.

3. The product assessment shall pay particular attention to the exposures, the risks and the efficacy linked to any uses covered by the application for authorisation but not addressed in the Union level risk assessment of the active substance.

Authorisations are subject to the following conditions:

1. For industrial or professional users, safe operational procedures and appropriate organizational measures shall be established. Where exposure cannot be reduced to an acceptable level by other means, products shall be used with appropriate personal protective equipment.
2. Persons making products containing medetomidine available on the market for non-professional users shall make sure that the products are supplied with appropriate gloves. Labels and, where provided, instructions for use shall

[3] See document: Note on the principles for taking decisions on the approval of active substances under the BPR (available from https://circabc.europa.eu/d/a/workspace/SpacesStore/c41b4ad4-356c-4852-9512-62e72cc919df/CA-March14-Doc.4.1%20-%20Final%20-%20Principles%20for%20substance%20approval.doc)
[4] See document: Further guidance on the application of the substitution criteria set out under article 10(1) of the BPR (available from https://circabc.europa.eu/d/a/workspace/SpacesStore/dbac71e3-cd70-4ed7-bd40-fc1cb92cfe1c/CA-Nov14-Doc.4.4%20-%20Final%20-%20Further%20guidance%20on%20Art10(1).doc)

indicate whether other personal protective equipment shall be used.Labels and, where provided, instructions for use shall indicate that children shall be kept away until treated surfaces are dry.

3. Labels and, where provided, safety data sheets of products authorised shall indicate that application, maintenance and repair activities shall be conducted within a contained area, on an impermeable hard standing with bunding or on soil covered with an impermeable material to prevent direct losses and minimize emissions to the environment, and that any losses or waste containing medetomidine shall be collected for reuse or disposal.
4. For products that may lead to residues in food or feed, the need to set new or to amend existing maximum residue levels (MRLs) in accordance with Regulation (EC) No 470/2009 of the European Parliament and of the Council[5] or Regulation (EC) No 396/2005 of the European Parliament and of the Council[6] shall be verified, and any appropriate risk mitigation measures shall be taken to ensure that the applicable MRLs are not exceeded.

Medetomidine gives rise to concern for both human health and the environment i.e. it is classified with acute toxicity of category 2 and toxic to aquatic life of acute category 1. Consequently, according to Article 28(2)(a) of Regulation (EU) No 528/2012, inclusion in Annex I of Regulation (EU) 528/2012 is not acceptable.

2.4. Elements to be taken into account when authorising products

1. The active substance medetomidine is considered as a candidate for substitution, and consequently the competent authority shall perform a comparative assessment as part of the evaluation of an application for either national or Union authorisation.
2. With regard to professional operator exposure, labelling should indicate the level of personal protective equipment including respiratory protective equipment that must be worn during handling, application and removal of products containing medetomidine.
3. Safe uses to the environment have been identified for scenarios representative of shipping lanes and the wider environment (i.e. areas adjacent to commercial harbours and marinas). A risk has been identified within marinas and commercial harbours. These areas may need additional consideration at national level and the available best practices shall be applied to mitigate these risks.
4. With regard to the environment, the need to address any specific national conditions and protection goals and/or undertake regional assessments should be considered at product authorisation stage, as environmental risk assessments in this evaluation have been based on generic EU scenarios.

2.5. Requirement for further information

Sufficient data have been provided to verify the conclusions on the active substance, permitting the proposal for the approval of medetomidine. However, further data are required:

Chemistry

The following data must be provided prior to the product authorisation stage:

[5] OJ L 152, 16.6.2009, p. 11.
[6] OJ L 70, 16.3.2005, p. 1

- For the monitoring method for sea water a further ion transition must be fully validated or a fully validated confirmatory method of analysis must be provided.

- For the monitoring method for plasma a second ion transition must be fully validated or a fully validated confirmatory method of analysis must be provided.

- For the monitoring method for sediment example chromatograms (standard, fortified sample and unfortified sample) must be provided. Recovery data must be generated at the LOQ and 10 x LOQ in order to assess the repeatability of the method. Five replicates at each level must be generated. A further ion transition must be fully validated or a fully validated confirmatory method of analysis must be provided.

- For the monitoring method for fish and shell fish a further ion transition must be fully validated or a confirmatory method must be provided.

- A method for air must be provided with an appropriate LOQ. The LOQ should comply with the requirements (concentration C) as outlined in the addendum to the TNsG (2009).

- The batch analysis data are from a pilot plant. Hence GLP batch analysis data from full scale production must be provided once this has commenced and stabilised.

These data must be provided to the eCA (UK) as soon as possible, but no later than at the date of approval of the active substance.

Environment

In order to address a potentially severe underestimation of the risk to sediment dwelling organisms from exposure via suspended matter, caused by the fact that sorption data (Koc) has only been studied at concentrations that are not fully relevant in the marine environment, a new study on sorption at environmentally relevant conditions (concentrations µg/l to ng/l, pH ~8, DOC not too high, etc.) is to be performed before the antifouling active substances are evaluated for a potential renewal of the approval.

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