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## **EU Risk Management Plan for Modafinil Bluefish (Modafinil)**

### **RMP version to be assessed as part of this application:**

RMP Version number: 3.0

Data lock point for this RMP: 2022-07-08

Date of final sign-off: 2022-08-16

**Rationale for submitting an updated RMP:** The updated RMP is submitted as per CMDh minutes for the meeting on 20-21 April 2022 published on 2022-05-19 (EMA/CMDh/366893/2022).

**Summary of significant changes in this RMP:** Updated Risk management plan to implement under Part III.1 and Annex 4, targeted follow-up questionnaire(s) to aid data capture from cases on drug abuse, misuse, dependence and diversion.

### **Other RMP versions under evaluation:**

RMP Version number: Not applicable

Submitted on: Not applicable

Procedure number: Not applicable

### **Details of the currently approved RMP:**

Version number: 2.1

Approved with procedure: IE/H/1088/001-002/R/001

Date of approval (opinion date): 2021-05-27

Deputy QPPV name: [REDACTED]

Deputy QPPV signature:



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## Abbreviations

<b>ATC</b>	Anatomical Therapeutic Chemical
<b>CMDh</b>	Coordination Group for Mutual Recognition and Decentralised Procedures – Human
<b>EEA</b>	European Economic Area
<b>EU</b>	European Union
<b>QPPV</b>	Qualified Person Responsible for Pharmacovigilance in the EU
<b>RMP</b>	Risk Management Plan
<b>SmPC</b>	Summary of Product Characteristics
<b>PRAC</b>	Pharmacovigilance Risk Assessment Committee
<b>CMS</b>	Concerned Member State
<b>RMS</b>	Reference Member State
<b>DE</b>	Germany
<b>ES</b>	Spain
<b>NL</b>	Netherlands
<b>SE</b>	Sweden
<b>UK</b>	United Kingdom
<b>MAH</b>	Marketing Authorisation Holder



## Table Part I.1 – Product Overview

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	<p>Lactose Povidone K30 (E1201) Sodium Stearyl Fumarate Silica, Colloidal Anhydrous (E551) Talc (E553b)</p> <p>Excipients with known effect: Lactose</p>
<b>Hyperlink to the Product Information</b>	Please refer to Module 1.3.1 SmPC, Labelling and Package Leaflet, common combined in Sequence 0000
<b>Indication(s) in the EEA</b>	<p><u>Current:</u> Modafinil is indicated in adults for the treatment of excessive sleepiness associated with narcolepsy with or without cataplexy.</p> <p>Excessive sleepiness is defined as difficulty maintaining wakefulness and an increased likelihood of falling asleep in inappropriate situations.<sup>1</sup></p>
	<p><u>Proposed (if applicable):</u> Not Applicable</p>
<b>Dosage in the EEA</b>	<p><u>Current:</u> Treatment should be initiated by or under the supervision of a physician with appropriate knowledge of indicated disorders.</p> <p>A diagnosis of narcolepsy should be made according to the International Classification of Sleep Disorders (ICSD2) guideline.</p> <p>Patient monitoring and clinical assessment of the need for treatment should be performed on a periodic basis.</p> <p><b>Posology</b></p> <p>The recommended starting daily dose is 200 mg. The total daily dose may be taken as a single dose in the morning or as two doses in the morning and at noon, according to physician assessment of the patient and the patient's response.</p> <p>Doses of up to 400mg in one or two divided doses can be used in patients with insufficient response to the initial 200mg modafinil dose.</p> <p><b>Long-term use</b></p> <p>Physicians prescribing modafinil for an extended time should periodically re-evaluate the long-term use for the individual patients as the long-term efficacy of modafinil has not been evaluated (&gt; 9 weeks).<sup>1</sup></p>
	<p><u>Proposed (if applicable):</u> Not applicable</p>



<b>Pharmaceutical form(s) and strengths</b>	<u>Current (if applicable):</u> Tablets; 100 mg Tablets; 200 mg
	<u>Proposed (if applicable):</u> Not applicable
<b>Is/will the product be subject to additional monitoring in the EU?</b>	No



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## **Part II: Safety specification**

### **PART II: Module SI - Epidemiology of the indication(s) and target population(s)**

Not applicable for generic products according to GVP Module V Rev.2



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## **PART II: Module SII - Non-clinical part of the safety specification**

Not applicable for generic products according to GVP Module V Rev.2



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## **PART II: Module SIII - Clinical trial exposure**

Not applicable for generic products according to GVP Module V Rev.2



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## **PART II: Module SIV - Populations not studied in clinical trials**

Not applicable for generic products according to GVP Module V Rev.2



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## **PART II: Module SV - Post-authorisation experience**

### **SV. I Post-authorisation exposure**

Not Applicable



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## **PART II: Module SVI - Additional EU requirements for the safety specification**

Not applicable for generic products according to GVP Module V Rev.2



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## **PART II: Module SVII - Identified and potential risks**

No new data in comparison to the information of the reference medicinal product is available.



## **PART II: Module SVIII - Summary of the safety concerns**

The updated modafinil RMP has been submitted as per EMA/CMDh/366893/2022 (CMDh minutes for the meeting on 20-21 April 2022 published on 2022-05-19).<sup>2</sup>

Table SVIII.1: Summary of safety concerns

<b>Summary of safety concerns</b>	
<b>Important identified risks</b>	Serious skin reactions
	Cardiovascular disorders
	Psychiatric disorders (including suicide/suicidal behaviour)
	Nervous system disorders
	Hypersensitivity
	Teratogenicity
<b>Important potential risks</b>	Misuse, abuse and diversion
	Off-label use (including off-label paediatric use)
<b>Missing information</b>	Use in elderly



## Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

### III.1 Routine pharmacovigilance activities

As a part of the routine pharmacovigilance activities, new safety data will be closely monitored for the events serious rash, including Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis and Drug Rash with Eosinophilia and Systemic Symptoms, cardiovascular disorder (risk), psychiatric related events such as anxiety, suicidal attempts and ideation, psychotic or manic symptoms, worsening of aggressive or hostile behaviour and depression, nervous system disorders, hypersensitivity, teratogenicity, misuse, abuse and diversion, off-label use (including off-label paediatric use), use in elderly and evaluated to further characterise these risks. Any new data leading to a change in the benefit-risk profile of the product will immediately be notified to the competent authorities.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

- **Specific adverse reaction follow-up questionnaire:**

- Drug abuse, misuse, dependence and diversion to aid in data capture from cases containing these events.

- **Other forms of routine pharmacovigilance activities for modafinil:**

No other forms of routine pharmacovigilance activities are considered necessary.

### III.2 Additional pharmacovigilance activities

Additional pharmacovigilance requirements are not considered necessary and routine pharmacovigilance activities are considered sufficient to monitor the benefit-risk profile of the product and detect any safety concerns.

### III.3 Summary table of additional pharmacovigilance activities

Not applicable



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## **Part IV: Plans for post-authorisation efficacy studies**

No PAES studies have been conducted and none are considered required.



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## **Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)**

### **Risk Minimisation Plan:**

The safety information in the proposed product information is aligned to the reference medicinal product Modafinil Cephalon, Cephalon FRANCE.



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## **Part VI: Summary of the risk management plan**

A separate RMP Part VI is provided below.



# Summary of risk management plan for Modafinil Bluefish (modafinil)

This is a summary of the risk management plan (RMP) for Modafinil Bluefish. The RMP details important risks of Modafinil Bluefish, which can be minimized through routine pharmacovigilance activities.

Modafinil Bluefish's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Modafinil Bluefish should be used.

Important new concerns or changes to the current ones will be included in updates of Modafinil Bluefish's RMP.

## I. The medicine and what it is used for

Modafinil Bluefish is indicated in adults for the treatment of excessive sleepiness associated with narcolepsy with or without cataplexy (see SmPC for the full indication). It contains modafinil as the active substance and it is given as oral tablets.

## II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Modafinil Bluefish, together with measures to minimise such risks about Modafinil Bluefish's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Modafinil Bluefish is not yet available, it is listed under 'missing information' below.

### II.A List of important risks and missing information

Important risks of Modafinil Bluefish are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken.

Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Modafinil Bluefish. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this



association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

<b>List of important risks and missing information</b>	
<b>Important identified risks</b>	Serious skin reactions
	Cardiovascular disorders
	Psychiatric disorders (including suicide/suicidal behaviour)
	Nervous system disorders
	Hypersensitivity
	Teratogenicity
<b>Important potential risks</b>	Misuse, abuse and diversion
	Off-label use (including off-label paediatric use)
<b>Missing information</b>	Use in elderly

## **II.B Summary of important risks**

The safety information in the proposed Product Information is aligned to the reference medicinal product Modafinil Cephalon, Cephalon FRANCE.

## **II.C Post-authorisation development plan**

### **II.C.1 Studies which are conditions of the marketing authorisation**

There are no studies which are conditions of the marketing authorisation or specific obligation of Modafinil Bluefish.

### **II.C.2 Other studies in post-authorisation development plan**

There are no studies required for Modafinil Bluefish



## Part VII: Annexes

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***Annex 1 - EudraVigilance Interface***

Available in electronic format only (available upon request).



***Annex 2 - Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme***

Not applicable



***Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan***

Not applicable



**Annex 4 - Specific adverse drug reaction follow-up forms**

	<b>TARGETED FOLLOW-UP QUESTIONNAIRE FOR ABUSE, MISUSE, DEPENDENCE AND DIVERSION - MODAFINIL</b>
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<b>Date of birth:</b>  <b>Initials:</b>	<b>Gender:</b> <input type="checkbox"/> Male <input type="checkbox"/> Female	<b>Weight in Kgs:</b> Is patient obese if weight is unknown: <input type="checkbox"/> Yes <input type="checkbox"/> No	<b>ARGUS CASE ID</b> <b>(To be entered by Bluefish):</b>
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**Description of the Event:**

Was the patient prescribed modafinil by his/her doctor?    Yes ☐    No ☐

Was the diagnosis:

Narcolepsy                      Yes ☐    No ☐    Don't know ☐

Please specify the diagnosis \_\_\_\_\_ and date of diagnosis:

\_\_\_\_\_

Please provide the relevant details below:

Modafinil dose prescribed	Route of administration	Duration of treatment
Concomitant medications prescribed	Route of administration	Duration of treatment

Was the patient intentionally taking modafinil without being prescribed by his/her doctor or in excess of what was prescribed?    Yes ☐    No ☐

*If yes, what was the intention*

*(please tick as appropriate):*

☐ To feel high / achieve a desirable psychological or physiological effect

☐ For weight loss



- ☐ For enhancing memory / concentration
- ☐ To treat excessive sleepiness better or faster
- ☐ To prevent withdrawal or any undesirable psychological or physiological effect
- ☐ If Other, Please specify \_\_\_\_\_

Please provide the relevant details below:

Modafinil dose taken	Route of administration (If oral please specify if swallowed intact / crushed / chewed / dissolved)	Duration and frequency of use

Has the patient used any illicit or prescription drugs concomitantly with modafinil, without being prescribed by his/her doctor or in excess of what was prescribed? Yes ☐ No ☐

*If yes, which ones*

*(please tick as appropriate):*

- ☐ Marijuana (pot)
- ☐ Methamphetamines (speed, meth, ice, crystal)
- ☐ LSD (acid)
- ☐ MDMA (Ecstasy)
- ☐ Rohypnol (roofies)
- ☐ Heroin (smack, junk)
- ☐ Cocaine/Crack (coke, snow)
- ☐ MDMA (Ecstasy)
- ☐ Ketamine (special K, vitamin K)
- ☐ Anabolic Steroids (Juice, gym candy)
- ☐ Benzodiazepines (diazepam and alprazolam)
- ☐ Stimulants (dextroamphetamine, methylphenidate, and amphetamine)
- ☐ Opioids (morphine, fentanyl)
- ☐ If Other, Please specify \_\_\_\_\_

Please provide the relevant details below:

Drug and dose taken	Route of administration	Duration and frequency of use



<p>Has the patient experienced any problems due to taking modafinil, without being prescribed by his/her doctor or in excess of what was prescribed? Yes <input type="checkbox"/> No <input type="checkbox"/></p> <p><i>If yes, which ones</i> <i>(please tick as appropriate):</i></p> <p><input type="checkbox"/> Unable to stop use when advised</p> <p><input type="checkbox"/> "blackouts" or "flashbacks" as a result of use</p> <p><input type="checkbox"/> Complaints / conflicts regarding use from family and friends</p> <p><input type="checkbox"/> Complaints / conflicts at work</p> <p><input type="checkbox"/> Use of drug in hazardous situations</p> <p><input type="checkbox"/> Medical problems as a result of use</p> <p><input type="checkbox"/> Need for increased doses to achieve the same effects over time</p> <p><input type="checkbox"/> Symptoms of overdose like insomnia, restlessness, disorientation, confusion, agitation, anxiety, excitation and hallucination, nausea and diarrhoea, tachycardia, bradycardia, hypertension and chest pain.</p> <p><input type="checkbox"/> Legal issues as a result of use or illegal possession or distribution</p> <p><input type="checkbox"/> If Other, Please specify _____</p>
--

<b>Event Outcome</b>	<b>Yes</b>	<b>No</b>
<p>Did the event resolve?</p> <ul style="list-style-type: none"> <li>• <i>If yes</i>, please specify event duration: _____ Minutes _____ Hours _____ Days</li> <li>• <i>If the event did not resolve</i>, please specify outcome:</li> </ul> <p>Resolved with sequelae <input type="checkbox"/></p> <p>Fatal <input type="checkbox"/></p> <p>Unknown <input type="checkbox"/></p> <p>Other <input type="checkbox"/></p> <p>If Other, Please specify _____</p>	<input type="checkbox"/>	<input type="checkbox"/>

<b>Action Taken with modafinil (please tick as appropriate)</b>		
<p>Daily dose:</p> <p>Last Dose Value: _____ Date: _____ Time: _____</p>		
	<b>Yes</b>	<b>No</b>
Was modafinil therapy withdrawn?	<input type="checkbox"/>	<input type="checkbox"/>



<i>If yes, did events resolve following this action?</i> If events resolved, please specify time to resolution: _____	<input type="checkbox"/>	<input type="checkbox"/>
If modafinil was re-administered to the patient after the event was resolved? <i>If yes, did the events recur upon re-administration of modafinil?</i>	<input type="checkbox"/>	<input type="checkbox"/>
If events recurred, please specify time to recurrence		

<b>Diagnostic Tests:</b>					
<b>Laboratory tests</b>	<b>Normal</b>	<b>Abnormal</b>	<b>Test not done</b>	<b>Results</b>	<b>Dates</b>
Urine Drug test	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
Blood toxicology test	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		

<b>Medical History and Adverse Event Details</b>	<b>Response</b>
<p>Reported medical history:</p> <p>When was abuse/misuse/dependence/diversion reported (dd-mmm-yyyy)?</p> <p>When did the treatment with modafinil begin?</p> <p>Was there a prior history of any type of abuse/misuse/dependence/diversion? If yes, please provide details:</p> <p>Was there a prior treatment for any type of abuse/misuse/dependence/diversion? If yes, please provide details:</p> <p>What are the patient's other medical history, psychiatric history (including history of dependence or abuse of other substances like alcohol / nicotine) and concurrent illnesses?</p> <p>Please include dates and treatments.</p>	



What other risk factors/alternative aetiology are present in the patient's profile that may have contributed to the development of abuse/misuse/dependence/diversion?	
Reported adverse event: Was the patient hospitalized for the adverse event(s)?  If yes, dates (dd-mmm-yyyy) of hospitalization and final diagnosis for the adverse event(s): Date (dd-mmm-yyyy) of discharge:	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown
If not hospitalized, did the patient seek treatment at an emergency room or medical office? Please specify (include dates):	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown



***Annex 5 - Protocols for proposed and on-going studies in RMP part IV***

Not applicable



***Annex 6 - Details of proposed additional risk minimisation activities (if applicable)***

Not applicable



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***Annex 7 - Other supporting data (including referenced material)***

1. Summary of Product Characteristics: Modafinil Bluefish.
2. EMA/CMDh/366893/2022 (CMDh minutes for the meeting on 20-21 April 2022 published on 2022-05-19) <https://www.hma.eu/457.html>



### ***Annex 8 - Summary of changes to the risk management plan over time***

<b>Versio n</b>	<b>Approval date Procedure</b>	<b>Change</b>
2.0	IE/H/1088/001-002/DC (2020-09-22)	<p>RMS transfer from Czech Republic to Ireland (procedure number updated)</p> <p><u>Safety concerns</u></p> <p><b>Important identified risks deleted:</b></p> <ul style="list-style-type: none"> <li>• Leukopenia</li> <li>• Eosinophilia</li> <li>• Hypercholesterolaemia</li> <li>• Hyperglycaemia</li> <li>• Diabetes mellitus</li> <li>• Paraesthesia</li> <li>• Dyskinesia</li> <li>• Hypertonia</li> <li>• Hyperkinesia</li> <li>• Amnesia</li> <li>• Migraine</li> <li>• Tremor</li> <li>• Vertigo</li> <li>• Hypoaesthesia</li> <li>• Movement disorder</li> <li>• Speech disorder</li> <li>• Blurred vision</li> <li>• Hypertension</li> <li>• Hypotension</li> <li>• Vasodilatation</li> <li>• Dyspnoea</li> <li>• Asthma</li> <li>• Dysphagia</li> <li>• Mouth ulcers</li> <li>• Glossitis</li> <li>• Myasthenia</li> <li>• Cramps</li> <li>• Acne</li> <li>• Twitch</li> <li>• Menstrual disorders</li> <li>• Chest pain</li> <li>• Peripheral oedema</li> <li>• Abnormal liver function tests, increases in alkaline phosphatase and gamma glutamyl transferase</li> <li>• Abnormal ECG</li> <li>• Anxiety</li> <li>• Suicide-related behaviour</li> <li>• Psychotic or manic symptoms</li> <li>• Aggressive or hostile behaviour</li> <li>• Use in patients with severe hepatic impairment</li> </ul>



		<ul style="list-style-type: none"> <li>• Hypersensitivity reactions</li> <li>• Drug interaction with steroidal contraceptives</li> <li>• Insomnia</li> <li>• Use in patients with lactose intolerance</li> <li>• Interaction with drugs metabolised by CYP2D6, CYP2C9 and CYP3A4/5</li> </ul> <p><b>Important identified risks amended:</b></p> <ul style="list-style-type: none"> <li>• Serious skin reactions – the following wording has been removed: (including Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis and Drug Rash with Eosinophilia and Systemic Symptoms)</li> <li>• Hypersensitivity reactions changed to hypersensitivity</li> </ul> <p><b>Important identified risks added:</b></p> <ul style="list-style-type: none"> <li>• Cardiovascular disorders</li> <li>• Psychiatric disorders (including suicide/suicidal behaviour)</li> <li>• Nervous system disorders</li> </ul> <p><b>Important potential risks amended:</b></p> <ul style="list-style-type: none"> <li>• Off-label use has been amended to include the following: Off label use (including off-label paediatric use)</li> </ul> <p><b>Missing information deleted:</b></p> <ul style="list-style-type: none"> <li>• Use in patients with renal impairment</li> <li>• Use in children</li> <li>• Long term use</li> </ul> <p><b>Missing information amended:</b></p> <ul style="list-style-type: none"> <li>• Use in pregnancy, lactation and fertility has been changed to an important potential risks.</li> </ul> <p><u>Risk minimisation measures:</u> Additional risk minimisation 1:</p> <ul style="list-style-type: none"> <li>• Added Direct Healthcare Professional Communication for the potential risk of exposure during pregnancy.</li> </ul> <p><u>Annexes</u></p> <ul style="list-style-type: none"> <li>• Annex 6: Details of proposed additional risk minimisation activities</li> </ul>
2.1	IE/H/1088/001-002/R/001 (2021-05-27)	<ul style="list-style-type: none"> <li>• Part II: In Module SVIII Section the important potential risk of 'Use during pregnancy and congenital abnormalities' has been replaced by the important identified risk 'Teratogenicity'. Module SV-Updated Post-authorisation exposure.</li> </ul>



		<ul style="list-style-type: none"> <li>Revised RMP version 2,1 is prepared as per modafinil Chanelle RMP 2.1</li> <li>Part I: In product review section few changes are made.</li> <li>In Part V: The risk minimisation section is updated to "Not applicable", since the DHPC distribution is completed in Ireland on 2020-10-28.</li> <li>Annexes section 6: Updated to Not applicable</li> </ul>
3.0	IE/H/1088/001-002/DC (Not Applicable)	<ul style="list-style-type: none"> <li>Updated risk management plan as per EMA/CMDh/366893/2022 (CMDh minutes for the meeting on 20-21 April 2022 published on 2022-05-19).</li> </ul> <p>Description of major changes:</p> <ul style="list-style-type: none"> <li>Updated Annex 4 and Part III.1 with targeted follow-up questionnaire to aid data capture from cases on drug abuse, misuse, dependence and diversion.</li> </ul>