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Human Medicines Evaluation

EU Risk Management Plan for METARAMINOLO MONICO (Metaraminol Bitartrate)

RMP version to be assessed as part of this application: 0.1

RMP Version number: 0.1

Data lock point for this RMP: 1st June 2020

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Rationale for submitting an updated RMP: Not applicable because initial marketing authorisation application submission

Summary of significant changes in this RMP: Initial Submission – update information according do DL

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23 GIU. 2020

[1] QPPV name will not be redacted in case of an access to documents request; see HMA/EMA Guidance document on the identification of commercially confidential information and personal data within the structure of the marketing-authorisation application; available on EMA website http://www.ema.europa.eu

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Part I: Product(s) Overview

Table Part I.1 – Product(s) Overview

Active substance(s) **(INN or common name)**	Metaraminol (metaraminol bitartrate)
Pharmacotherapeutic group(s) (ATC Code)	C01CA09
Marketing Authorisation Holder	Monico SpA via Ponte di Pietra 7 30173 – Venezia Mestre
Medicinal products to which this RMP refers	/
Invented name(s) in the European Economic Area (EEA)	Aramine
Marketing authorisation procedure	National
Brief description of the product	Chemical class 3,β-dihydroxyamphetamine: it acts a simpatomimetic agent but doesn't contain the catechol group
	Summary of mode of action Metaramol is a sympathomimetic agent, actin both in alfa- and beta-adrenoreceptors. Anyway, the effect of beta-receptor is more potent and so the principal effect of metaraminolo is the vasoconstriction that determines both systolic and diastolic blood pressure. The effect is similar to norepinephrine but the action is more lasting. Metaraminol acts as a false-neurotransmitter so it is undergone to re-uptake, storage and extraction as an endogenous catecholamines.
	Important information about its composition The solution contains sodium metabisulfite: in some individuals, this molecule can induce severe allergic reaction or bronchospasm.
Hyperlink to the Product Information	Patient Information Leaflet hyperlink
Indication(s) in the EEA	Current: treatment of the acute hypotension due to an insufficient vasoconstrictor tone as per spinal anaesthesia, alone or combined

	with other medicinals
	Proposed (if applicable): not applicable
Dosage in the EEA	Current: 5 to 100 mg diluted in normal saline of glucose 5%, by intravenous infusion. In life treating procedure, the injection directly into a vain of 0.5 to 5 mg could be applied
	Proposed (if applicable): not applicable
Pharmaceutical form(s) and strengths	Current (if applicable): solution for injection and infusion
	Proposed (if applicable):
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Not applicable – well-establish use application

Part II: Module SII - Non-clinical part of the safety specification

Not applicable – well-establish use application

Part II: Module SIII - Clinical trial exposure

Not applicable – well-establish use application

Part II: Module SIV - Populations not studied in clinical trials

Not applicable – well-establish use application

Part II: Module SV - Post-authorisation experience

Not applicable – well-establish use application

Part II: Module SVI - Additional EU requirements for the safety specification

Not applicable – well-establish use application

Part II: Module SVII - Identified and potential risks

Metaraminol is a sympathomimetic agent acting as a false neurotransmitter: its effects are similar to those of norepinephrine even if it is less potent but the effect its more long lasting.

Because the medicinal follows the same pathways of endogenous catecholamine, the overall effects is an increasing of adrenergic activity.

The risks associated with the use of the medicinal are mainly related to an exceeding sympathomimetic effect, in genre due to an overdose (hypertension, bradycardia due to hypertension, cardiac arrhythmias, tissue necrosis or desquamation, nausea, headache and palpitation).

Cardiac arrhythmias (essential or due to hypertension) and hypertension have to be considered as important risks.

The local and cutaneous effects are related to vasoconstriction, they are reversible by the discontinuation. Symptoms (mainly due to hypertension) are not serious, do not require pharmacological treatment and are resolved by the reduction of the blood pressure.

SVII.1 Identification of safety concerns in the initial RMP submission

As reported in the above paragraph, metaraminol acts as a false neurotransmitter, for this reason it shares the safety concerns with the catecholamines (in particular norepinephrine) used in therapy.

The medicinal is of well-established use so the safety issues can be considered well-known and indicated in the SmPC published by authority.

Hypertension and headache are considered very common during the administration of metaraminol, but headache may be considered as a consequence of hypertension.

Hypertension may lead to other side signs and symptoms: they are reported in the SmPC as bradycardia, tachycardia and other cardiac arrhythmias, that can lead to serious consequences, also to death.

Because of the side effects are related to an excess of the therapeutic effect, overdosage must be taken into consideration: in this case sings and symptoms are ascribable to an excess of sympathetic activity as severe cardiac arrhythmia that can develop in cardiac arrest, myocardiac infarction, pulmonary oedema and/or convulsion.

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

The following risks are not included in the list of the safety concerns:

- headache

- palpitations, sensation of chest constriction

- abscesses formation

- tissue necrosis
- skin desquamation
- nausea, vomiting
- euphoria, diaphoresis

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Headache is not included because it is a symptom of hypertension. The reduction of the infusion rate resolves hypertension and then the headache. Even if this symptom seems to be frequent, it is related to stimulation/hyperstimulation of sympathetic system: any other drug used for increase the blood pressure (catecholamine in genre) shares this adverse reaction because of vascular constriction. Moreover, because of the medicinal is used for the treatment of acute hypotension during anaesthesia, headache seems not to impact the benefit/risk ratio. It is also important to notice that headache permits the rapid identification of high blood pressure values, helping the fast recognition of hypertension.

Palpitations and sensation of chest constriction are both related to the administration of a sympathetic agent. They are symptoms acceptable in respective to the treatment.

Also euphoria and diaphoresis are related to a hyper stimulation of the adrenergic system: in these cases, a reduction of the infusion rate resolves the signs.

Abscesses are developed by the infiltration of microorganisms under epidermis and they may occur when a parenteral administration is used. Along with tissue necrosis and skin desquamation, the adverse reactions above mentioned may be caused by hypoxia due to vasoconstriction, in genre near the site of injection. These effects are well-known and foreseeable on the basis of the pharmacological action of the active ingredient: these effects are also possible with all the other vasopressor agents used for the treatment of hypotension. The frequency of these adverse effects are not stated, they may be related to medical error (higher doses, extravasation, poor hygiene).

Nausea and vomiting are common in the administration of any medicinal, and they may arise from many different sourcess (physiological or psychological), by the medical procedure, by the other medicinal used in concomitance.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

IMPOTRANT IDENTIFIED RISKS

Hypertension: it may develop for an excess of activity of the medicinal. Because the medicinal is in genre administered by infusion and the infusion rate must be evaluated by the physician according to the clinical response, a exceeding dosage may occur. Hypertension may rapidly resolve by the reduction of the infusion rate or by discontinuation of the administration. Anyway, hypertension may be severe if not rapidly recognized and eventually treated by the use of alfa-blocker agent. The pre-existing cardiac pathology, hypertension or hyperthyroidism and diabetes may increase the risk of

hypertension. Because the acute hypotension determines hypo-perfusion to shock, the risk is considered acceptable in comparison to the benefit expected.

Risk-benefit impact: hypertension is a serious adverse reaction because it can lead to pulmonary oedema, cardiac arrhythmias and cardiac arrest. Because of the above mentioned reason, the adverse reaction is stated frequent, according to the SmPC.

Cardiac arrhythmias: adrenergic agents may cause disturbance on the cardiac rhythm, both by a direct stimulation of the myocardial conduction system (as tachycardia or other arrhythmias) or following hypertension (as bradycardia). Cardiac arrhythmias can be resolved by the discontinuation of the administration or by the reduction of the infusion rate. Digitalis, I-MAO and halogen anaesthetic can make myocardial more susceptible to this adverse effect.

Risk-benefit impact: the frequency of arrhythmia is unknown, anyway it is a consequence of the hyper stimulation. Even if cardiac arrhythmias may lead to serious outcome (as cardiac arrest, see below) the monitoring of the blood pressure – along with the registration of the symptoms of the patient – allow the rapid identification of an exceeding adrenergic stimulation. This adverse reaction is also reported for all the other adrenergic agents used as sympathetic agonists, so cardiac arrhythmia is a potential side effect shared with all the molecules of this class. Taking into consideration that hypertension may lead itself to cardiac disorders and shock (potentially fatal), the benefit/risk ratio has to be considered positive.

Myocardial infarction/cardiac arrest: the frequency is stated as unknown in the SmPC. The sympathetic stimulation may result in a coronary spasm instead of a vasodilatation and lead to ischemia, infarction or cardiac arrest as other simulating agent, that may be exacerbated by hypertension

Risk-benefit impact: as reported above, the correct dosing of the medicinal may avoid-reduce the risks of onset of the myocardial damage.

Pulmonary oedema: pulmonary oedema is a well-known consequence of pulmonary hypertension, developed by the same pharmacological base described above. Pulmonary oedema may cause hypoxia.

Risk-benefit impact: as reported above, the correct dosing of the medicinal may avoid-reduce the risks of onset of the pulmonary oedema.

Convulsion: it is a consequence of a severe over-dosage.

Risk-benefit impact: as reported above, the correct dosing of the medicinal may avoid-reduce the risks of onset of the convulsion.

IMPORTANT POTENTIAL RISKS

Because the risks are evaluated on the basis of the SmPC published my MHRA, all the risks are considered "identified".

MISSING INFORMATION

<Pregnant woman>

There are no well-controlled studies in pregnant women. Accodingly to the SmPC, Metaraminol should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the foetus.

<Breatfeeing>

It is not known whether metaraminol is secreted in human milk . Because many drugs are secreted in human milk and no information are available on exposure of children by breastfeeding, caution should be exercised if metaraminol is given to a breastfeeding mother.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable, medicinal not approved yet.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Hypertension

Potential mechanisms: metaraminol is an alfa- and beta-adrenoceptors agonist. Its effect is more potent towards beta-receptor so vasoconstriction along with inotropic effect on the heart are predominant: this results in an increase of blood pressure. Because of the therapeutic dose of the medicinal is wide, it is difficult to estimate the correct dosage and hypertension may occur

Evidence source(s) and strength of evidence: the risks is reported in the SmPC published by MHRA and it is indicated as frequent.

Characterisation of the risk: severe hypertension can be lead to severe consequences such as pulmonary oedema, cardia arrhythmias, cardiac arrest, until to death.

Hypertension can be frequent because of the wide therapeutic range and because the rate of administration is related to the response of the patient.

Risk factors and risk groups: no specific groups are identified, but elderlies are more susceptible to the action of adrenergic agent. Moreover, patients undergone I-MAO therapy can have an excessive response to metaramiol.

Preventability: hypertension is nor predictable. Anyway, the continuous monitoring of the blood pressure is useful to verify the efficacy of the drug and to evaluate the infusion rate: in this condition hypotension may be identified early.

Impact on the risk-benefit balance of the product: hypertension arises for an excessive activity of the drug (patient particular susceptible to the drug, exceeding infusion rate/dose). All the sympathetic

drugs share with metaraminolo this side effect. The effect of metaraminolo can be modulated by the infusion rate or the infusion can be discontinued in case of severe hypertension.

Public health impact: this safety concern is based on the SmPC published by MHRA. No further information is available.

Cardiac Arrhythmias

Potential mechanisms: metaraminol has a potent effect on the stimulation of beta-adrenoceptors, leading to inotropic and chronotropic positive effect. The excessive stimulation may lead to tachycardia and other conductivity disorders. Bradycardia is a reflex effect of hypertension by baroreceptor stimulation.

Evidence source(s) and strength of evidence: the risk is reported in the SmPC published by MHRA and it is indicated as frequency unknown.

Characterisation of the risk: cardiac arrhythmias can lead to cardiac arrest and death.

Risk factors and risk groups: no specific groups are identified. Leanne cirrhosis has been associated in one patient with fatal ventricular arrhythmia. Medicinals that can increase the susceptibility of myocardium to the action of adrenergic drug are – for example – digitalis, halothane and cyclopropane, and I-MAO.

Preventability: cardiac arrhythmias are nor predictable, but can be more frequent in patient with pre-existent cardiac disorders. The use of the medicinal above mentioned may increase the possibility of onset of cardiac dosorders.

Impact on the risk-benefit balance of the product: the frequency of cardiac arrhytmias is repoted as unknown. All the sympathetic drugs share with metaraminolo this side effect. The effect of metaraminolo can be modulated by the infusion rate or the infusion can be discontinued in case of cardiac disorders.

Public health impact: this safety concern is based on the SmPC published by MHRA. No further information is available.

Myocardial infarction/myocardial arrest

Potential mechanisms: even if the adrenergic drugs induce release of the coronary vessels, high doses may induce vasospasm that can lead to myocardial infarction and then cardiac arrest.

Evidence source(s) and strength of evidence: the risk is reported in the SmPC published by MHRA and it is indicated as frequency unknown. The pharmacological effect is reported in literature and it is common in the abuse of adrenergic drug as amphetamine.

Characterisation of the risk: myocardial infarction may lead to death.

Risk factors and risk groups: no specific groups are identified, but elderlies are more susceptible to the action of adrenergic agents. It is reported a case of fatal ventricular arrhythmia in a patient with Leanne cirrhosis.

Preventability: myocardial infarction and arrest are nor predictable.

Impact on the risk-benefit balance of the product: myocardial infarction and arrest arise from an excessive activity of the drug (patient particular susceptible to the drug, exceeding infusion rate/dose). All the sympathetic drugs may have the same effect.

Public health impact: this safety concern is based on the SmPC published by MHRA. No further information is available.

Pulmonary oedema

Potential mechanisms: the activation of beta-adrenoceptors leads to constrinction of the pulmonary arteries. The increase of pressure into the artery branch of the small circulation stimulates the passage of water from the plasma into the alveoli.

Evidence source(s) and strength of evidence: the risks is reported in the SmPC published by MHRA and it is indicated in the overdosage consequence.

Characterisation of the risk: pulmonary oedema rarely is fatal because of the slow onset. If treated by the reduction of the medicinal (and eventually diuretics) it is resolved rapidly.

Risk factors and risk groups: no specific groups are identified, but elderlies are more susceptible to the action of adrenergic agent.

Preventability: pulmonary oedema is a consequence of hypertension. The control of blood pressure and of the infusion rate can avoid this adverse reaction.

Impact on the risk-benefit balance of the product: pulmonary oedema arises for an excessive activity of the drug (patient particular susceptible to the drug, exceeding infusion rate/dose). All the sympathetic drugs may have the same effect.

Public health impact: this safety concern is based on the SmPC published by MHRA. No further information is available.

Convulsion

Potential mechanisms: convulsion is side effect of severe hypertension, whatever the cause

Evidence source(s) and strength of evidence: the risk is reported in the SmPC published by MHRA and it is indicated in the overdosage consequence.

Characterisation of the risk: convulsion is not fatal but may it be very uncomfortable for the patient and ca be dangerous in some people. It can be treated by the infusion of diazepam (elective first approach for the treatment of convulsion)

Risk factors and risk groups: no specific groups are identified, but elderlies are more susceptible to the action of adrenergic agent.

Preventability: convulsion is a consequence of severe of hypertension. The control of the blood pressure and of the infusion rate can avoid this adverse reaction.

Impact on the risk-benefit balance of the product: convulsion arises from an excessive activity of the drug (patient particular susceptible to the drug, exceeding infusion rate/dose).

Public health impact: this safety concern is based on the SmPC published by MHRA. No further information is available.

SVII.3.2. Presentation of the missing information

Not applicable

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• hypertension • cardiac arrhythmias • myocardial infarction/myocardial arrest • pulmonary oedema • convulsion
Important potential risks	/
Missing information	• Pregnant women • Breastfeeding

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

III.1 Routine pharmacovigilance activities

The routine pharmacovigilance activities are adequate to fulfil pharmacovigilance obligation.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires: none

Other forms of routine pharmacovigilance activities for: hypertension, cardia arrhythmias, cardiac arrest/infarction, pulmonary oedema, convulsion.

According to the present RMP, these ADRs must be collected by the MAH and periodically evaluated for the identification of new safety concerns or the modification of the seriousness/frequency of the already known ADRs.

III.2 Additional pharmacovigilance activities

None

III.3 Summary Table of additional Pharmacovigilance activities

None

Part IV: Plans for post-authorisation efficacy studies

None

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

Risk Minimisation Plan

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Hypertension	*Routine risk communication:* SmPC section 4.8 and PL section 2 *Routine risk minimisation activities recommending specific clinical measures to address the risk:* • a recommendation to regulate the infusion rate accordingly to the blood pressure value is added in SmCP section 4.2 (PIL section 2) • recommendation regarding the use of the medicinal in older patients (more susceptible to the effect of the medicinal) is introduced at SmPC section 4.2 and at PIL section 2 • a statement to not use Metaraminol in patient with hypertension, thyroid disorders or diabetes mellitus is present at section 4.4 of the SmPC (section 2 of the PIL and section for healthcare professional) • a warning about the concomitant use of I-MAO is present at section 4.5 of the SmC (section 2 of the PIL) *How to early identified increased blood pressure:* • a statement is introduced in SmPC section 4.4 suggesting to apply a continuous monitoring of blood pressure in order to early identify the onset of hypertension (section 2 of the PIL and section for healthcare professional) *How to treat hypertension:* • the use of alpha-blocker is suggested to treat over-dosage (resulting in hypertension) at section 4.9 of the SmPC; in the PIL a generic statement is reported. In the section for the professional health care the information about the treatment of hypertension are reported

	(section for healthcare profession of the PIL)
Cardiac arrhythmias	*Routine risk communication:* • recommendation to use precaution in the use of the medicinal in patient with cirrhosis (and in particular Leanne's cirrhosis) is present at SmPC section 4.2 and 4.8, PIL because this clinical condition seems to be associated with ventricular arrhythmia • recommendation regarding the use of the medicinal in older patients (more susceptible to the effect of the medicinal) is introduced at SmPC section 4.2 and at PIL section 2 • a reccomandation to avoid the use of metaraminol in patient underwent digitalis is present at section 4.5 of the SmPC and at PIL section 2 • a warning about the concomitant use of MAO-I is present at section 4.5 of the SmPC (section 2 of the PIL) *How to treat arrhythmias:* • the indication to reduce the infusion rate in case of the extra systoles is reported at section 4.4 of the SmPC
myocardial infarction/ myocardial arrest	*Routine risk communication:* • at section 4.8 of the SmPC the cardiac disturbances are reported, along with indication of the risk associated to patients undergone myocardial infarction (section 3 of the PIL) • at section 4.9 of the SmPC a statement about myocardial infarction and myocardial arrest (due to over dosage) is present along with other disturbances of the cardiac rhythm (section 4 of the PIL) *How to treat myocardial infarction/arrest:* • the discontinuation of the administration or the application of ice at the site of subcutaneous/intramuscular injection is reported at point 4.9 of the SmPC (section for healthcare professional fo the PIL)
Pulmonary oedema	*Routine risk communication:* • at section 4.4 of the SmPC pulmonary oedema is reported as a consequence of the increase of blood pressure caused by hypertension (Section 3 of the PIL) *How to prevent/treat pulmonary oedema:* • because pulmonary oedema is a consequence of hypertension, the warning about prevention and treatment of hypertension are applicable, as reported at point 4.9 of the SmPC (dection 4 of the PIL)

Convulsion	*Routine risk communication:* • at section 4.9 of the SmPC convulsion is stated to be related to an overdosage of the medicinal (section 3 of the PIL) *How to treat convulsion:* • the use of diazepam to solve convulsion in reported at section 4.9 of the SmPC (section for healthcare professional of the PIL)
Pregnant woman	*Routine risk communication:* • the lack of information about the use of the medicinal in pregnant woman is reported at section 4.6 of he SmPC (section 2 of the PIL)
Breastfeeding	*Routine risk communication:* • the lack of information about the use of the medicinal during breastfeeding is reported at section 4.6 of he SmPC (section 2 of the PIL)

Part VI: Summary of the risk management plan

Summary of risk management plan for Metaraminolo Monico (materaminol)

This is a summary of the risk management plan (RMP) for Metaraminolo Monico. The RMP details important risks of Metaraminolo Monico, how these risks can be minimised, and how more information will be obtained about Metaraminolo Monico's risks and uncertainties (missing information).

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

I. The medicine and what it is used for

Metaraminolo Monico is authorised for treatment of the acute hypotension due to an insufficient vasoconstrictor tone as per spinal anaesthesia, alone or combined with other medicinals. It contains metaraminolo bitartrate as the active substance and it is given by intravenous injection or infusion, after proper dilution

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

Important risks of Metaraminolo Monico, together with measures to minimise such risks and the proposed studies for learning more about Metaraminolo Monico'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.

II.A List of important risks and missing information

Important risks of Metaraminolo Monico are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. 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 Metaraminolo Monico. 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);

List of important risks and missing information	
Important identified risks	• hypertension • cardiac arrhythmias • myocardial infarction/myocardial arrest • pulmonary oedema • convulsion
Important potential risks	/
Missing information	• Pregnant women • Breastfeeding

II.B Summary of important risks

Important identified risk: hypertension	
Evidence for linking the risk to the medicine	the risks is reported in the SmPC published by MHRA and it is indicated as frequent.
Risk factors and risk groups	no specific groups are identified, but elderlies are more susceptible to the action of adrenergic agent. Moreover, patients undergone I-MAO therapy can have an excessive response to metaramiol.
Risk minimisation measures	No risk minimisation measures

Important identified risk: Cardiac Arrhythmias	
Evidence for linking the risk to the medicine	The risk is reported in the SmPC published by MHRA and it is indicated as frequency unknown.
Risk factors and risk groups	No specific groups are identified. Leanne cirrhosis has been associated in one patient with fatal ventricular arrhythmia. Medicinals that can increase the susceptibility of myocardium to the action of adrenergic drug are – for example – digitalis, halothane and cyclopropane, and I-MAO.
Risk minimisation measures	No risk minimisation measures

Important identified risk: Myocardial infarction/myocardial arrest	
Evidence for linking the risk to the medicine	The risk is reported in the SmPC published by MHRA and it is indicated as frequency unknown. The pharmacological effect is reported in literature and it is common in the abuse of adrenergic drug as amphetamine.
Risk factors and risk groups	No specific groups are identified, but elderlies are more susceptible to the action of adrenergic agents. It is reported a case of fatal ventricular arrhythmia in a patient with Leanne cirrhosis.
Risk minimisation measures	No risk minimisation measures

Important identified risk: Pulmonary oedema	
Evidence for linking the risk to the medicine	The risks is reported in the SmPC published by MHRA and it is indicated in the overdosage consequence.
Risk factors and risk groups	No specific groups are identified, but elderlies are more susceptible to the action of adrenergic agent.
Risk minimisation measures	No risk minimisation measures>

Important identified risk: Convulsion	
Evidence for linking the risk to the medicine	The risk is reported in the SmPC published by MHRA and it is indicated in the overdosage consequence.
Risk factors and risk groups	No specific groups are identified, but elderlies are more susceptible to the action of adrenergic agent.
Risk minimisation measures	No risk minimisation measures

Missing information: Pregnant woman	
Risk minimisation measures	No risk minimisation measures

Missing information: Breastfeeding	
Risk minimisation measures	No risk minimisation measures

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 Metaraminolo Monico

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

There are no studies required for Metaraminolo Monico

Part VII: Annexes

Table of contents

Annex 1 – EudraVigilance Interface

Not applicable

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

Not applicable

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

Annex 7 - Other supporting data (including referenced material)

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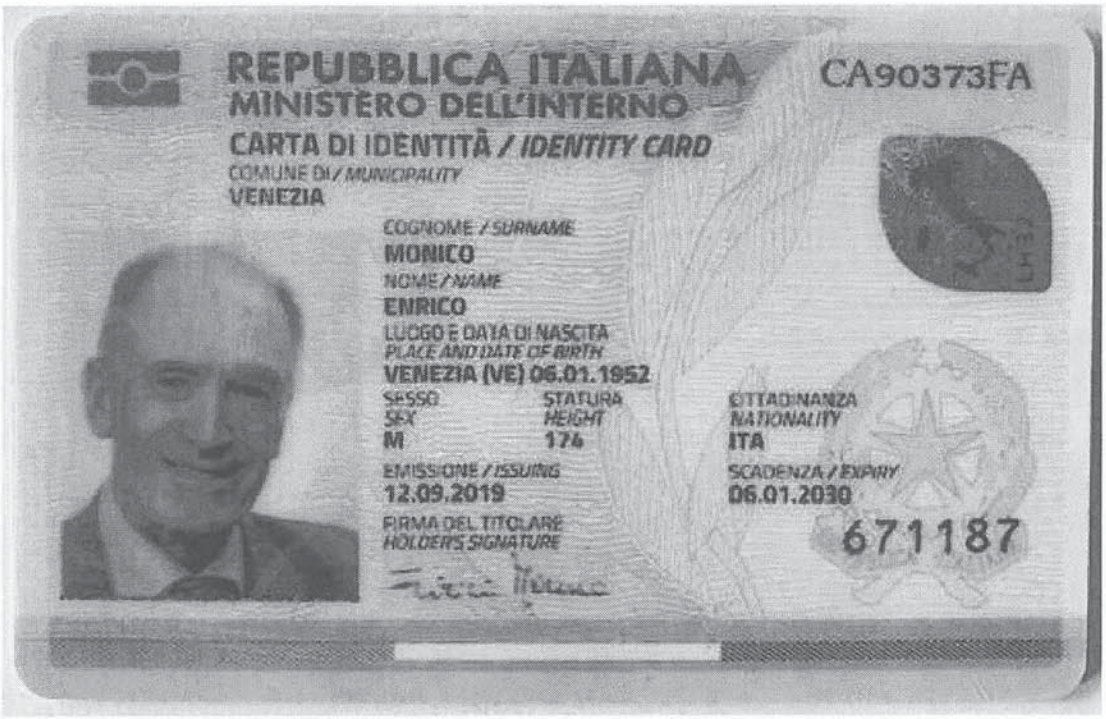
Annex 8 – Summary of changes to the risk management plan over time

Version	**Approval date** **Procedure**	**Change**
0.0	At the time of authorisation 01/06/2020	First submission for Marketing authorization
0.1	At the time of authorisation 01/06/2020	Changes as per AIFA requests



REPUBBLICA ITALIANA
MINISTERO DELL'INTERNO
CARTA DI IDENTITÀ / *IDENTITY CARD*
COMUNE DI / *MUNICIPALITY*
VENEZIA

CA90373FA

COGNOME / *SURNAME*
MONICO
NOME / *NAME*
ENRICO
LUOGO E DATA DI NASCITA
PLACE AND DATE OF BIRTH
VENEZIA (VE) 06.01.1952
SESSO / *SEX*: M
STATURA / *HEIGHT*: 174
CITTADINANZA / *NATIONALITY*: ITA
EMISSIONE / *ISSUING*: 12.09.2019
SCADENZA / *EXPIRY*: 06.01.2030
FIRMA DEL TITOLARE
HOLDER'S SIGNATURE
671187

COGNOME E NOME DEL PADRE E DELLA MADRE O DI CHI NE FA LE VECE
FATHER AND MOTHER'S TUTOR'S NAME

CODICE FISCALE
FISCAL CODE
MNCNRC52A06L736G

ESTREMI ATTO DI NASCITA
80 p1 sA-1952 027042

INDIRIZZO DI RESIDENZA / *RESIDENCE*
SESTIERE CASTELLO (VENEZIA),N. 5653 VENEZIA (VE)

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