Part VI: Summary of the risk management plan

Summary of risk management plan for Ephedrine Meduna 10 mg/ml, solution for injection (Ephedrine Hydrochloride)

This is a summary of the risk management plan (RMP) for Ephedrine Meduna 10 mg/ml, solution for injection. The RMP details important risks of Ephedrine Meduna 10 mg/ml, solution for injection, how these risks can be minimised, and how more information will be obtained about Ephedrine Meduna 10 mg/ml, solution for injection's risks and uncertainties (missing information).

Ephedrine Meduna 10 mg/ml, solution for injection's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Ephedrine Meduna 10 mg/ml, solution for injection should be used.

Important new concerns or changes to the current ones will be included in updates of Ephedrine Meduna 10 mg/ml, solution for injection 's RMP.

I. The medicine and what it is used for

Ephedrine Meduna 10 mg/ml, solution for injection is authorised for treatment of hypotension from spinal or epidural anaesthesia and during general anaesthesia, with or without a reduction in the heart rate, administered for a surgical or obstetric procedure (see SmPC for the full indication). It contains Ephedrine Hydrochloride as the active substance and it is given by i.v administration.

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

Important risks of Ephedrine HCl 10 mg/ml, solution for injection, together with measures to minimise such risks and the proposed studies for learning more about Ephedrine HCl 10 mg/ml, solution for injection'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*.

II.A List of important risks and missing information

Important risks of Ephedrine HCl 10 mg/ml, solution for injection 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 Ephedrine HCl 10 mg/ml, solution for injection. 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.

List of important risks and missing information	
Important identified risks	Overdosage
	Tachycardia and cardiac arrhythmias
	Hypertension (crisis of)
	Acute urinary retention
	Phaeochromocytoma
	Arteriosclerosis
	Aneurysm
Important potential risks	Neonatal tachycardia and Acidosis
	Teratogenicity in early pregnancy
Missing information	None

II.B Summary of important risks

Overdosage	
Evidence for linking the risk to the medicine	Overdose reactions which may appeared after the administration of Ephedrine can be associated with severe complications for patients that could be led in rare cases, even to lethal complications. Clinicians who administer the drug must be aware about its correct dose regimen and the patient conditions and on how to promptly recognise overdose symptoms and know treatment options.
Risk factors and risk groups	The risk group can be considered the elderly patients, mainly due to co-morbidities and preexisting medication.
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.2 and 4.9.* *PIL section 3.* *SmPC Section 4.2, 4.9 and PIL section 3 where the advice*

	is given on how to correctly administer ephedrine and manage early symptoms of overdose.

Tachycardia and cardiac arrhythmias	
Evidence for linking the risk to the medicine	Tachycardia and cardiac arrhythmias are adverse reactions which may appeared after the administration of Ephedrine can be associated with severe complications for patients but the outcomes are not fatal in normal patients. Clinicians who administer the drug must be aware about its correct dose regimen and the patient conditions and on how to promptly recognise cardiac symptoms and know treatment options.
Risk factors and risk groups	Elderly patients and concomitant cardiac disorders are risky situation in the administration of ephedrine. Anesthesiologists have the knowledge to use the suitable lower dose in case of hypotension during anesthesia.
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.4, 4.5, 4.8, 4.9* *PIL section 3, 4.* *SmPC section 4.4 where advice is given on monitoring specific patients.* *SmPC section 4.5 where advise is given on possible interactions with other medicinal products.* *SmPC section 4.9and PIL section 3 where advice is given on how to detect early signs and symptoms of tachycardia and cardiac arrhythmias.*

Hypertension (crisis of)	
Evidence for linking the risk to the medicine	Crisis of hypertension is an adverse reaction which may appeared after the administration of Ephedrine can be associated with severe complications for patients but the outcomes are not fatal in normal patients. Clinicians who administer the drug must be aware about its correct dose regimen and the patient conditions and on how to promptly recognise early symptoms and know treatment options.
Risk factors and risk groups	Elderly patients and concomitant chronic hypertension are risky situation in the administration of ephedrine. Anesthesiologists have the knowledge to use suitable lower dose in case of hypotension during anesthesia and manage

	the side effect, hypertension, in case of occurrence.
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.3, 4.4, 4.5, 4.8, 4.9.* *PIL section 2, 3, 4.* *SmPC section 4.3 and PIL section 2 where advice is given on contraindications on the use of the medicinal product.* *SmPC section 4.4 and PIL section 2 where advice is given on monitoring specific patients.* *SmPC section 4.5 where advise is given on possible interactions with other medicinal products.* *SmPC section 4.9 where advice is given on how to detect early signs and symptoms of hypertension and hypertensive crisis.*

Acute urinary retention	
Evidence for linking the risk to the medicine	Acute urinary retention is an adverse reaction which may appeared after the administration of Ephedrine.
Risk factors and risk groups	Elderly and prostatic hyperplasic patients are in a risky situation. Anesthesiologists have the knowledge to use suitable lower dose of ephedrine in case of elderly patient and prostatic hyperplasia as reported in preventability section.
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.8.* *PIL section 4.*

Phaeochromocytoma	
Evidence for linking the risk to the medicine	Pheochromocytomas are rare, reportedly occurring in 0.05–0.2% of hypertensive individuals. This accounts for only a portion of cases, however, as patients may be completely asymptomatic. A retrospective study from the Mayo Clinic revealed that in 50% of cases of pheochromocytoma, the diagnosis was made at autopsy. Approximately 10% of pheochromocytomas are discovered incidentally.
Risk factors and risk groups	Pheochromocytomas occur in people of all races, although they are diagnosed less frequently in blacks. Pheochromocytomas may occur in persons of any age, but

	the peak incidence is from the third to the fifth decades of life. Approximately 10% occur in children, a pediatric subset where ephedrine use is not allowed. Fifty percent of pheochromocytomas in children are solitary intra-adrenal lesions, 25% are present bilaterally, and 25% are extra-adrenal.
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.3.* *PIL section 2.* *SmPC section 4.3 and PIL section 2 where advice is given on contraindications on the use of the medicinal product.*

Arteriosclerosis	
Evidence for linking the risk to the medicine	The incidence, prevalence, and manifestations of Coronary Artery Disease (CAD) vary significantly with race, as does the response to therapy. Coronary artery atherosclerosis is the principal cause of coronary artery disease (CAD), in which atherosclerotic changes are present within the walls of the coronary arteries. CAD is a progressive disease process that generally begins in childhood and manifests clinically in middle to late adulthood.
Risk factors and risk groups	Age is the strongest risk factor for the development of CAD. Most cases of CAD become clinically apparent in patients aged 40 years or older, but elderly persons experience higher mortality and morbidity rates from it.
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.3.* *PIL section 2.* *SmPC section 4.3 and PIL section 2 where advice is given on contraindications on the use of the medicinal product.*

Aneurysm	
Evidence for linking the risk to the medicine	An aneurysm occurs when part of a blood vessel (artery) or cardiac chamber swells, either the blood vessel is damaged or there is a weakness in the wall of the blood vessel. As the aneurysm grows there is a greater risk of rupture; this can lead to severe haemorrhage, and other complications, including sudden death. A hypertensive crisis due to an overdosage of ephedrine can precipitate the swelling of

	aneurysm.
Risk factors and risk groups	Different risk factors may concur to the development of aneurysm such as race, sex and age.
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.3.* *PIL section 2.* *SmPC section 4.3 and PIL section 2 where advice is given on contraindications on the use of the medicinal product.*

Neonatal tachicardia and acidosis	
Evidence for linking the risk to the medicine	Several articles discussed the possible association of ephedrine and signs of neonatal tachycardia and acidosis. However, for this particular Important Potential Risk it is not possible to find data of evidence of the risk in the unexposed target population. As a matter of fact, in order to find this particular risk, all the patients have to be in the same condition of parturient, that is the exposed population. Not only pregnant women that have to undergo to cesarean section can be treated with ephedrine, but only pregnant women could develop neonatal tachycardia and acidosis; due to this it is not possible to find the risk in the unexposed target population.
Risk factors and risk groups	Pregnant women undergoing caesarean delivery performed under spinal anaesthesia.
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.6.* *PIL section 2.* *SmPC section 4.6 and PIL section 2 where advice is given on contraindication and specific warning on the use of the medicinal product.*

Teratogenicity in early pregnancy	
Evidence for linking the risk to the medicine	The use of ephedrine in pregnancy should be avoided as ephedrine crossed the placenta and this has been associated with an increase in fetal heart rate and beat-to-beat variability. The distribution of outcomes is not available. Tabulate grades of severity are not available in

	human studies. No data have been found in international literature on the percentage of recovered with or without treatment or sequelae, furthermore there aren't evidence in literature of the percentage of hospitalized for teratogenicity in early pregnancy.
Risk factors and risk groups	Pregnant women.
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.6.* *PIL section 2.* *SmPC section 4.6 and PIL section 2 where advice is given on contraindication and specific warning on the use of the medicinal product.*

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 Ephedrine Meduna 10 mg/ml, solution for injection.

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

There are no studies required for Ephedrine Meduna 10 mg/ml, solution for injection.

Summary of risk management plan for Ephedrine Meduna 50 mg/ml, solution for injection (Ephedrine Hydrochloride)

This is a summary of the risk management plan (RMP) for Ephedrine Meduna 50 mg/ml, solution for injection. The RMP details important risks of Ephedrine Meduna 50 mg/ml, solution for injection, how these risks can be minimised, and how more information will be obtained about Ephedrine Meduna 50 mg/ml, solution for injection's risks and uncertainties (missing information).

Ephedrine Meduna 50 mg/ml, solution for injection's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Ephedrine Meduna 50 mg/ml, solution for injection should be used.

Important new concerns or changes to the current ones will be included in updates of Ephedrine Meduna 50 mg/ml, solution for injection 's RMP.

I. The medicine and what it is used for

Ephedrine Meduna 50 mg/ml, solution for injection is authorised for treatment of hypotension from spinal or epidural anaesthesia and during general anaesthesia, with or without a reduction in the heart rate, administered for a surgical or obstetric procedure (see SmPC for the full indication). It contains Ephedrine Hydrochloride as the active substance and it is given by i.v administration.

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

Important risks of Ephedrine HCl 50 mg/ml, solution for injection, together with measures to minimise such risks and the proposed studies for learning more about Ephedrine HCl 50 mg/ml, solution for injection'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*.

II.A List of important risks and missing information

Important risks of Ephedrine HCl 50 mg/ml, solution for injection 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 Ephedrine HCl 50 mg/ml, solution for injection. 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.

List of important risks and missing information	
Important identified risks	Overdosage
	Tachycardia and cardiac arrhythmias
	Hypertension (crisis of)
	Acute urinary retention
	Phaeochromocytoma
	Arteriosclerosis
	Aneurysm
Important potential risks	Neonatal tachycardia and Acidosis
	Teratogenicity in early pregnancy
Missing information	None

II.B Summary of important risks

Overdosage	
Evidence for linking the risk to the medicine	Overdose reactions which may appeared after the administration of Ephedrine can be associated with severe complications for patients that could be led in rare cases, even to lethal complications. Clinicians who administer the drug must be aware about its correct dose regimen and the patient conditions and on how to promptly recognise overdose symptoms and know treatment options.
Risk factors and risk groups	The risk group can be considered the elderly patients, mainly due to co-morbidities and preexisting medication.
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.2 and 4.9.* *PIL section 3.* *SmPC Section 4.2, 4.9 and PIL section 3 where the advice*

	is given on how to correctly administer ephedrine and manage early symptoms of overdose.

Tachycardia and cardiac arrhythmias	
Evidence for linking the risk to the medicine	Tachycardia and cardiac arrhythmias are adverse reactions which may appeared after the administration of Ephedrine can be associated with severe complications for patients but the outcomes are not fatal in normal patients. Clinicians who administer the drug must be aware about its correct dose regimen and the patient conditions and on how to promptly recognise cardiac symptoms and know treatment options.
Risk factors and risk groups	Elderly patients and concomitant cardiac disorders are risky situation in the administration of ephedrine. Anesthesiologists have the knowledge to use the suitable lower dose in case of hypotension during anesthesia.
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.4, 4.5, 4.8, 4.9* *PIL section 3, 4.* *SmPC section 4.4 where advice is given on monitoring specific patients.* *SmPC section 4.5 where advise is given on possible interactions with other medicinal products.* *SmPC section 4.9and PIL section 3 where advice is given on how to detect early signs and symptoms of tachycardia and cardiac arrhythmias.*

Hypertension (crisis of)	
Evidence for linking the risk to the medicine	Crisis of hypertension is an adverse reaction which may appeared after the administration of Ephedrine can be associated with severe complications for patients but the outcomes are not fatal in normal patients. Clinicians who administer the drug must be aware about its correct dose regimen and the patient conditions and on how to promptly recognise early symptoms and know treatment options.
Risk factors and risk groups	Elderly patients and concomitant chronic hypertension are risky situation in the administration of ephedrine. Anesthesiologists have the knowledge to use suitable lower dose in case of hypotension during anesthesia and manage

	the side effect, hypertension, in case of occurrence.
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.3, 4.4, 4.5, 4.8, 4.9.* *PIL section 2, 3, 4.* *SmPC section 4.3 and PIL section 2 where advice is given on contraindications on the use of the medicinal product.* *SmPC section 4.4 and PIL section 2 where advice is given on monitoring specific patients.* *SmPC section 4.5 where advise is given on possible interactions with other medicinal products.* *SmPC section 4.9 where advice is given on how to detect early signs and symptoms of hypertension and hypertensive crisis.*

Acute urinary retention	
Evidence for linking the risk to the medicine	Acute urinary retention is an adverse reaction which may appeared after the administration of Ephedrine.
Risk factors and risk groups	Elderly and prostatic hyperplasic patients are in a risky situation. Anesthesiologists have the knowledge to use suitable lower dose of ephedrine in case of elderly patient and prostatic hyperplasia as reported in preventability section.
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.8.* *PIL section 4.*

Phaeochromocytoma	
Evidence for linking the risk to the medicine	Pheochromocytomas are rare, reportedly occurring in 0.05–0.2% of hypertensive individuals. This accounts for only a portion of cases, however, as patients may be completely asymptomatic. A retrospective study from the Mayo Clinic revealed that in 50% of cases of pheochromocytoma, the diagnosis was made at autopsy. Approximately 10% of pheochromocytomas are discovered incidentally.
Risk factors and risk groups	Pheochromocytomas occur in people of all races, although they are diagnosed less frequently in blacks. Pheochromocytomas may occur in persons of any age, but

	the peak incidence is from the third to the fifth decades of life. Approximately 10% occur in children, a pediatric subset where ephedrine use is not allowed. Fifty percent of pheochromocytomas in children are solitary intra-adrenal lesions, 25% are present bilaterally, and 25% are extra-adrenal.
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.3.* *PIL section 2.* *SmPC section 4.3 and PIL section 2 where advice is given on contraindications on the use of the medicinal product.*

Arteriosclerosis	
Evidence for linking the risk to the medicine	The incidence, prevalence, and manifestations of Coronary Artery Disease (CAD) vary significantly with race, as does the response to therapy. Coronary artery atherosclerosis is the principal cause of coronary artery disease (CAD), in which atherosclerotic changes are present within the walls of the coronary arteries. CAD is a progressive disease process that generally begins in childhood and manifests clinically in middle to late adulthood.
Risk factors and risk groups	Age is the strongest risk factor for the development of CAD. Most cases of CAD become clinically apparent in patients aged 40 years or older, but elderly persons experience higher mortality and morbidity rates from it.
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.3.* *PIL section 2.* *SmPC section 4.3 and PIL section 2 where advice is given on contraindications on the use of the medicinal product.*

Aneurysm	
Evidence for linking the risk to the medicine	An aneurysm occurs when part of a blood vessel (artery) or cardiac chamber swells, either the blood vessel is damaged or there is a weakness in the wall of the blood vessel. As the aneurysm grows there is a greater risk of rupture; this can lead to severe haemorrhage, and other complications, including sudden death. A hypertensive crisis due to an overdosage of ephedrine can precipitate the swelling of

	aneurysm.
Risk factors and risk groups	Different risk factors may concur to the development of aneurysm such as race, sex and age.
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.3.* *PIL section 2.* *SmPC section 4.3 and PIL section 2 where advice is given on contraindications on the use of the medicinal product.*

Neonatal tachicardia and acidosis	
Evidence for linking the risk to the medicine	Several articles discussed the possible association of ephedrine and signs of neonatal tachycardia and acidosis. However, for this particular Important Potential Risk it is not possible to find data of evidence of the risk in the unexposed target population. As a matter of fact, in order to find this particular risk, all the patients have to be in the same condition of parturient, that is the exposed population. Not only pregnant women that have to undergo to cesarean section can be treated with ephedrine, but only pregnant women could develop neonatal tachycardia and acidosis; due to this it is not possible to find the risk in the unexposed target population.
Risk factors and risk groups	Pregnant women undergoing caesarean delivery performed under spinal anaesthesia.
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.6.* *PIL section 2.* *SmPC section 4.6 and PIL section 2 where advice is given on contraindication and specific warning on the use of the medicinal product.*

Teratogenicity in early pregnancy	
Evidence for linking the risk to the medicine	The use of ephedrine in pregnancy should be avoided as ephedrine crossed the placenta and this has been associated with an increase in fetal heart rate and beat-to-beat variability. The distribution of outcomes is not available. Tabulate grades of severity are not available in

	human studies. No data have been found in international literature on the percentage of recovered with or without treatment or sequelae, furthermore there aren't evidence in literature of the percentage of hospitalized for teratogenicity in early pregnancy.
Risk factors and risk groups	Pregnant women.
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.6.* *PIL section 2.* *SmPC section 4.6 and PIL section 2 where advice is given on contraindication and specific warning on the use of the medicinal product.*

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 Ephedrine Meduna 50 mg/ml, solution for injection.

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

There are no studies required for Ephedrine Meduna 50 mg/ml, solution for injection.

Summary of risk management plan for Ephedrine Sintetica 10 mg/ml, solution for injection (Ephedrine Hydrochloride)

This is a summary of the risk management plan (RMP) for Ephedrine Sintetica 10 mg/ml, solution for injection. The RMP details important risks of Ephedrine Sintetica 10 mg/ml, solution for injection, how these risks can be minimised, and how more information will be obtained about Ephedrine Sintetica 10 mg/ml, solution for injection's risks and uncertainties (missing information).

Ephedrine Sintetica 10 mg/ml, solution for injection's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Ephedrine Sintetica 10 mg/ml, solution for injection should be used.

Important new concerns or changes to the current ones will be included in updates of Ephedrine Sintetica 10 mg/ml, solution for injection 's RMP.

I. The medicine and what it is used for

Ephedrine Sintetica 10 mg/ml, solution for injection is authorised for treatment of hypotension from spinal or epidural anaesthesia and during general anaesthesia in adults and children over 12 years (see SmPC for the full indication). It contains Ephedrine Hydrochloride as the active substance and it is given by i.v administration.

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

Important risks of Ephedrine HCl 10 mg/ml, solution for injection, together with measures to minimise such risks and the proposed studies for learning more about Ephedrine HCl 10 mg/ml, solution for injection'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*.

II.A List of important risks and missing information

Important risks of Ephedrine HCl 10 mg/ml, solution for injection 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 Ephedrine HCl 10 mg/ml, solution for injection. 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.

List of important risks and missing information	
Important identified risks	Overdosage
	Tachycardia and cardiac arrhythmias
	Hypertension (crisis of)
	Acute urinary retention
	Phaeochromocytoma
	Arteriosclerosis
	Aneurysm
Important potential risks	Neonatal tachycardia and Acidosis
	Teratogenicity in early pregnancy
Missing information	None

II.B Summary of important risks

Overdosage	
Evidence for linking the risk to the medicine	Overdose reactions which may appeared after the administration of Ephedrine can be associated with severe complications for patients that could be led in rare cases, even to lethal complications. Clinicians who administer the drug must be aware about its correct dose regimen and the patient conditions and on how to promptly recognise overdose symptoms and know treatment options.
Risk factors and risk groups	The risk group can be considered the elderly patients, mainly due to co-morbidities and preexisting medication.
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.2 and 4.9.* *PIL section 3.* *SmPC Section 4.2, 4.9 and PIL section 3 where the advice*

	is given on how to correctly administer ephedrine and manage early symptoms of overdose.

Tachycardia and cardiac arrhythmias	
Evidence for linking the risk to the medicine	Tachycardia and cardiac arrhythmias are adverse reactions which may appeared after the administration of Ephedrine can be associated with severe complications for patients but the outcomes are not fatal in normal patients. Clinicians who administer the drug must be aware about its correct dose regimen and the patient conditions and on how to promptly recognise cardiac symptoms and know treatment options.
Risk factors and risk groups	Elderly patients and concomitant cardiac disorders are risky situation in the administration of ephedrine. Anesthesiologists have the knowledge to use the suitable lower dose in case of hypotension during anesthesia.
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.4, 4.5, 4.8, 4.9* *PIL section 3, 4.* *SmPC section 4.4 where advice is given on monitoring specific patients.* *SmPC section 4.5 where advise is given on possible interactions with other medicinal products.* *SmPC section 4.9and PIL section 3 where advice is given on how to detect early signs and symptoms of tachycardia and cardiac arrhythmias.*

Hypertension (crisis of)	
Evidence for linking the risk to the medicine	Crisis of hypertension is an adverse reaction which may appeared after the administration of Ephedrine can be associated with severe complications for patients but the outcomes are not fatal in normal patients. Clinicians who administer the drug must be aware about its correct dose regimen and the patient conditions and on how to promptly recognise early symptoms and know treatment options.
Risk factors and risk groups	Elderly patients and concomitant chronic hypertension are risky situation in the administration of ephedrine. Anesthesiologists have the knowledge to use suitable lower dose in case of hypotension during anesthesia and manage

	the side effect, hypertension, in case of occurrence.
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.3, 4.4, 4.5, 4.8, 4.9.* *PIL section 2, 3, 4.* *SmPC section 4.3 and PIL section 2 where advice is given on contraindications on the use of the medicinal product.* *SmPC section 4.4 and PIL section 2 where advice is given on monitoring specific patients.* *SmPC section 4.5 where advise is given on possible interactions with other medicinal products.* *SmPC section 4.9 where advice is given on how to detect early signs and symptoms of hypertension and hypertensive crisis.*

Acute urinary retention	
Evidence for linking the risk to the medicine	Acute urinary retention is an adverse reaction which may appeared after the administration of Ephedrine.
Risk factors and risk groups	Elderly and prostatic hyperplasic patients are in a risky situation. Anesthesiologists have the knowledge to use suitable lower dose of ephedrine in case of elderly patient and prostatic hyperplasia as reported in preventability section.
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.8.* *PIL section 4.*

Phaeochromocytoma	
Evidence for linking the risk to the medicine	Pheochromocytomas are rare, reportedly occurring in 0.05–0.2% of hypertensive individuals. This accounts for only a portion of cases, however, as patients may be completely asymptomatic. A retrospective study from the Mayo Clinic revealed that in 50% of cases of pheochromocytoma, the diagnosis was made at autopsy. Approximately 10% of pheochromocytomas are discovered incidentally.
Risk factors and risk groups	Pheochromocytomas occur in people of all races, although they are diagnosed less frequently in blacks. Pheochromocytomas may occur in persons of any age, but

	the peak incidence is from the third to the fifth decades of life. Approximately 10% occur in children, a pediatric subset where ephedrine use is not allowed. Fifty percent of pheochromocytomas in children are solitary intra-adrenal lesions, 25% are present bilaterally, and 25% are extra-adrenal.
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.3.* *PIL section 2.* *SmPC section 4.3 and PIL section 2 where advice is given on contraindications on the use of the medicinal product.*

Arteriosclerosis	
Evidence for linking the risk to the medicine	The incidence, prevalence, and manifestations of Coronary Artery Disease (CAD) vary significantly with race, as does the response to therapy. Coronary artery atherosclerosis is the principal cause of coronary artery disease (CAD), in which atherosclerotic changes are present within the walls of the coronary arteries. CAD is a progressive disease process that generally begins in childhood and manifests clinically in middle to late adulthood.
Risk factors and risk groups	Age is the strongest risk factor for the development of CAD. Most cases of CAD become clinically apparent in patients aged 40 years or older, but elderly persons experience higher mortality and morbidity rates from it.
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.3.* *PIL section 2.* *SmPC section 4.3 and PIL section 2 where advice is given on contraindications on the use of the medicinal product.*

Aneurysm	
Evidence for linking the risk to the medicine	An aneurysm occurs when part of a blood vessel (artery) or cardiac chamber swells, either the blood vessel is damaged or there is a weakness in the wall of the blood vessel. As the aneurysm grows there is a greater risk of rupture; this can lead to severe haemorrhage, and other complications, including sudden death. A hypertensive crisis due to an overdosage of ephedrine can precipitate the swelling of

	aneurysm.
Risk factors and risk groups	Different risk factors may concur to the development of aneurysm such as race, sex and age.
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.3.* *PIL section 2.* *SmPC section 4.3 and PIL section 2 where advice is given on contraindications on the use of the medicinal product.*

Neonatal tachicardia and acidosis	
Evidence for linking the risk to the medicine	Several articles discussed the possible association of ephedrine and signs of neonatal tachycardia and acidosis. However, for this particular Important Potential Risk it is not possible to find data of evidence of the risk in the unexposed target population. As a matter of fact, in order to find this particular risk, all the patients have to be in the same condition of parturient, that is the exposed population. Not only pregnant women that have to undergo to cesarean section can be treated with ephedrine, but only pregnant women could develop neonatal tachycardia and acidosis; due to this it is not possible to find the risk in the unexposed target population.
Risk factors and risk groups	Pregnant women undergoing caesarean delivery performed under spinal anaesthesia.
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.6.* *PIL section 2.* *SmPC section 4.6 and PIL section 2 where advice is given on contraindication and specific warning on the use of the medicinal product.*

Teratogenicity in early pregnancy	
Evidence for linking the risk to the medicine	The use of ephedrine in pregnancy should be avoided as ephedrine crossed the placenta and this has been associated with an increase in fetal heart rate and beat-to-beat variability. The distribution of outcomes is not available. Tabulate grades of severity are not available in

	human studies. No data have been found in international literature on the percentage of recovered with or without treatment or sequelae, furthermore there aren't evidence in literature of the percentage of hospitalized for teratogenicity in early pregnancy.
Risk factors and risk groups	Pregnant women.
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.6.* *PIL section 2.* *SmPC section 4.6 and PIL section 2 where advice is given on contraindication and specific warning on the use of the medicinal product.*

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 Ephedrine Sintetica 10 mg/ml, solution for injection.

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

There are no studies required for Ephedrine Sintetica 10 mg/ml, solution for injection.

Summary of risk management plan for Ephedrine Sintetica 50 mg/ml, solution for injection (Ephedrine Hydrochloride)

This is a summary of the risk management plan (RMP) for Ephedrine Sintetica 50 mg/ml, solution for injection. The RMP details important risks of Ephedrine Sintetica 50 mg/ml, solution for injection, how these risks can be minimised, and how more information will be obtained about Ephedrine Sintetica 50 mg/ml, solution for injection's risks and uncertainties (missing information).

Ephedrine Sintetica 50 mg/ml, solution for injection's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Ephedrine Sintetica 50 mg/ml, solution for injection should be used.

Important new concerns or changes to the current ones will be included in updates of Ephedrine Sintetica 50 mg/ml, solution for injection 's RMP.

I. The medicine and what it is used for

Ephedrine Sintetica 50 mg/ml, solution for injection is authorised for treatment of hypotension from spinal or epidural anaesthesia and during general anaesthesia in adults and children over 12 years (see SmPC for the full indication). It contains Ephedrine Hydrochloride as the active substance and it is given by i.v administration.

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

Important risks of Ephedrine HCl 50 mg/ml, solution for injection, together with measures to minimise such risks and the proposed studies for learning more about Ephedrine HCl 50 mg/ml, solution for injection'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*.

II.A List of important risks and missing information

Important risks of Ephedrine HCl 50 mg/ml, solution for injection 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 Ephedrine HCl 50 mg/ml, solution for injection. 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.

List of important risks and missing information	
Important identified risks	Overdosage
	Tachycardia and cardiac arrhythmias
	Hypertension (crisis of)
	Acute urinary retention
	Phaeochromocytoma
	Arteriosclerosis
	Aneurysm
Important potential risks	Neonatal tachycardia and Acidosis
	Teratogenicity in early pregnancy
Missing information	None

II.B Summary of important risks

Overdosage	
Evidence for linking the risk to the medicine	Overdose reactions which may appeared after the administration of Ephedrine can be associated with severe complications for patients that could be led in rare cases, even to lethal complications. Clinicians who administer the drug must be aware about its correct dose regimen and the patient conditions and on how to promptly recognise overdose symptoms and know treatment options.
Risk factors and risk groups	The risk group can be considered the elderly patients, mainly due to co-morbidities and preexisting medication.
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.2 and 4.9.* *PIL section 3.* *SmPC Section 4.2, 4.9 and PIL section 3 where the advice*

	is given on how to correctly administer ephedrine and manage early symptoms of overdose.

Tachycardia and cardiac arrhythmias	
Evidence for linking the risk to the medicine	Tachycardia and cardiac arrhythmias are adverse reactions which may appeared after the administration of Ephedrine can be associated with severe complications for patients but the outcomes are not fatal in normal patients. Clinicians who administer the drug must be aware about its correct dose regimen and the patient conditions and on how to promptly recognise cardiac symptoms and know treatment options.
Risk factors and risk groups	Elderly patients and concomitant cardiac disorders are risky situation in the administration of ephedrine. Anesthesiologists have the knowledge to use the suitable lower dose in case of hypotension during anesthesia.
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.4, 4.5, 4.8, 4.9* *PIL section 3, 4.* *SmPC section 4.4 where advice is given on monitoring specific patients.* *SmPC section 4.5 where advise is given on possible interactions with other medicinal products.* *SmPC section 4.9and PIL section 3 where advice is given on how to detect early signs and symptoms of tachycardia and cardiac arrhythmias.*

Hypertension (crisis of)	
Evidence for linking the risk to the medicine	Crisis of hypertension is an adverse reaction which may appeared after the administration of Ephedrine can be associated with severe complications for patients but the outcomes are not fatal in normal patients. Clinicians who administer the drug must be aware about its correct dose regimen and the patient conditions and on how to promptly recognise early symptoms and know treatment options.
Risk factors and risk groups	Elderly patients and concomitant chronic hypertension are risky situation in the administration of ephedrine. Anesthesiologists have the knowledge to use suitable lower dose in case of hypotension during anesthesia and manage

	the side effect, hypertension, in case of occurrence.
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.3, 4.4, 4.5, 4.8, 4.9.* *PIL section 2, 3, 4.* *SmPC section 4.3 and PIL section 2 where advice is given on contraindications on the use of the medicinal product.* *SmPC section 4.4 and PIL section 2 where advice is given on monitoring specific patients.* *SmPC section 4.5 where advise is given on possible interactions with other medicinal products.* *SmPC section 4.9 where advice is given on how to detect early signs and symptoms of hypertension and hypertensive crisis.*

Acute urinary retention	
Evidence for linking the risk to the medicine	Acute urinary retention is an adverse reaction which may appeared after the administration of Ephedrine.
Risk factors and risk groups	Elderly and prostatic hyperplasic patients are in a risky situation. Anesthesiologists have the knowledge to use suitable lower dose of ephedrine in case of elderly patient and prostatic hyperplasia as reported in preventability section.
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.8.* *PIL section 4.*

Phaeochromocytoma	
Evidence for linking the risk to the medicine	Pheochromocytomas are rare, reportedly occurring in 0.05–0.2% of hypertensive individuals. This accounts for only a portion of cases, however, as patients may be completely asymptomatic. A retrospective study from the Mayo Clinic revealed that in 50% of cases of pheochromocytoma, the diagnosis was made at autopsy. Approximately 10% of pheochromocytomas are discovered incidentally.
Risk factors and risk groups	Pheochromocytomas occur in people of all races, although they are diagnosed less frequently in blacks. Pheochromocytomas may occur in persons of any age, but

	the peak incidence is from the third to the fifth decades of life. Approximately 10% occur in children, a pediatric subset where ephedrine use is not allowed. Fifty percent of pheochromocytomas in children are solitary intra-adrenal lesions, 25% are present bilaterally, and 25% are extra-adrenal.
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.3.* *PIL section 2.* *SmPC section 4.3 and PIL section 2 where advice is given on contraindications on the use of the medicinal product.*

Arteriosclerosis	
Evidence for linking the risk to the medicine	The incidence, prevalence, and manifestations of Coronary Artery Disease (CAD) vary significantly with race, as does the response to therapy. Coronary artery atherosclerosis is the principal cause of coronary artery disease (CAD), in which atherosclerotic changes are present within the walls of the coronary arteries. CAD is a progressive disease process that generally begins in childhood and manifests clinically in middle to late adulthood.
Risk factors and risk groups	Age is the strongest risk factor for the development of CAD. Most cases of CAD become clinically apparent in patients aged 40 years or older, but elderly persons experience higher mortality and morbidity rates from it.
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.3.* *PIL section 2.* *SmPC section 4.3 and PIL section 2 where advice is given on contraindications on the use of the medicinal product.*

Aneurysm	
Evidence for linking the risk to the medicine	An aneurysm occurs when part of a blood vessel (artery) or cardiac chamber swells, either the blood vessel is damaged or there is a weakness in the wall of the blood vessel. As the aneurysm grows there is a greater risk of rupture; this can lead to severe haemorrhage, and other complications, including sudden death. A hypertensive crisis due to an overdosage of ephedrine can precipitate the swelling of

	aneurysm.
Risk factors and risk groups	Different risk factors may concur to the development of aneurysm such as race, sex and age.
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.3.* *PIL section 2.* *SmPC section 4.3 and PIL section 2 where advice is given on contraindications on the use of the medicinal product.*

Neonatal tachicardia and acidosis	
Evidence for linking the risk to the medicine	Several articles discussed the possible association of ephedrine and signs of neonatal tachycardia and acidosis. However, for this particular Important Potential Risk it is not possible to find data of evidence of the risk in the unexposed target population. As a matter of fact, in order to find this particular risk, all the patients have to be in the same condition of parturient, that is the exposed population. Not only pregnant women that have to undergo to cesarean section can be treated with ephedrine, but only pregnant women could develop neonatal tachycardia and acidosis; due to this it is not possible to find the risk in the unexposed target population.
Risk factors and risk groups	Pregnant women undergoing caesarean delivery performed under spinal anaesthesia.
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.6.* *PIL section 2.* *SmPC section 4.6 and PIL section 2 where advice is given on contraindication and specific warning on the use of the medicinal product.*

Teratogenicity in early pregnancy	
Evidence for linking the risk to the medicine	The use of ephedrine in pregnancy should be avoided as ephedrine crossed the placenta and this has been associated with an increase in fetal heart rate and beat-to-beat variability. The distribution of outcomes is not available. Tabulate grades of severity are not available in

	human studies. No data have been found in international literature on the percentage of recovered with or without treatment or sequelae, furthermore there aren't evidence in literature of the percentage of hospitalized for teratogenicity in early pregnancy.
Risk factors and risk groups	Pregnant women.
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.6.* *PIL section 2.* *SmPC section 4.6 and PIL section 2 where advice is given on contraindication and specific warning on the use of the medicinal product.*

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 Ephedrine Sintetica 50 mg/ml, solution for injection.

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

There are no studies required for Ephedrine Sintetica 50 mg/ml, solution for injection.