PART VI SUMMARY OF ACTIVITIES IN THE RISK MANAGEMENT PLAN BY MEDICINAL PRODUCT

VI.1 Elements for summary tables in the European Public Assessment Report (EPAR)

VI.1.1 Summary table of safety concerns

Summary of safety concerns	
Important identified risks	• Hypersensitivity • Use in patients with renal impairment • Use in pregnancy and lactation • Use in neonates (less than three months of age) • Use in patients with glucose-6-phosphate dehydrogenase deficiency • Use in patients with acute porphyria • Pulmonary disorders • Hepatic impairment • Peripheral neuropathy and neurological disorders • Use in patients with diabetes mellitus • Use in patients with electrolyte imbalance • Haematological disorders including anaemia • Use in patients with debilitating conditions • Use in patients with vitamin B (particularly folate) deficiency • Gastrointestinal disturbances • Concomitant use with quinolone anti-infectives and typhoid vaccine • Effect on ability to drive and use machines
Important potential risks	• None
Missing information	• None

VI.1.2 Table of ongoing and planned studies in the post-authorisation pharmacovigilance development plan

Not applicable

VI.1.3 Summary of post-authorisation efficacy development plan

Not applicable

VI.1.4 Summary table of risk minimisation measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Important identified risks		
Hypersensitivity	The risks (1) associated with the use of the drug product in patients hypersensitive to nitrofurantoin or other nitrofurans and (2) associated with the use of the drug product in patients with history of allergic reactions are described in the SPC Sections 4.3, 4.4 and 4.8 and PIL Section 2, 4 and appropriate advice is provided to the prescriber to minimise these risks.	None
Use in patients with renal impairment	The risks (1) associated with the use of the drug product in patients with renal impairment, and (2) of concomitant use of the drug product with other medicinal products are described in the SPC Sections 4.1, 4.2, 4.3, 4.4 and 4.5and PIL Section 2, and appropriate advice is provided to the prescriber to minimise these risks.	None
Use in pregnancy and lactation	The risks associated with the use of the drug product in pregnancy and lactation, are described in the SPC Sections 4.3 and 4.6 and PIL Section 2 and appropriate advice is provided to the prescriber to minimise these risks.	None
Use in neonates (less than three months of age)	The risks associated with the use of the drug product in neonates (less than three months of age), are described in the SPC Sections 4.3 and 4.6 and PIL Sections 2, 3, and appropriate advice is provided to the	None

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
	prescriber to minimise these risks.	
Use in patients with glucose-6-phosphate dehydrogenase deficiency	The risks associated with the use of the drug product in patients with glucose-6-phosphate dehydrogenase deficiency are described in the SPC Sections 4.3, 4.4 and 4.8 and PIL Section 2 and appropriate advice is provided to the prescriber to minimise these risks.	None
Use in patients with acute porphyria	The risks associated with the use of the drug product in patients with acute porphyria are described in the SPC Sections 4.3, 4.8 and PIL Sections 2, and appropriate advice is provided to the prescriber to minimise these risks.	None
Pulmonary disorders	The risks (1) of pulmonary reactions associated with the use of the drug product and (2) associated with the use of drug product in patients with pulmonary disorders are described in the SPC Sections 4.4, 4.8 and PIL Sections 2, 3, 4 and appropriate advice is provided to the prescriber to minimise these risks.	None
Hepatic impairment	The risks (1) of hepatic impairment associated with the use of the drug product and (2) associated with the use of drug product in patients with hepatic impairment, and (3) associated with the concomitant use of the drug product with oestrogen-containing contraceptives are described in the SPC Sections 4.4, 4.5, 4.8 and PIL Sections 2, 3, 4 and appropriate advice is provided to the prescriber to minimise these	None

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
	risks.	
Peripheral neuropathy and neurological disorders	The risks (1) of peripheral neuropathy associated with the use of the drug product and (2) associated with the use of drug product in patients with neurological disorders are described in the SPC Sections 4.4, 4.8 and PIL Sections 2, 3, 4 and appropriate advice is provided to the prescriber to minimise these risks.	None
Use in patients with diabetes mellitus	The risks associated with the use of the drug product in patients with diabetes mellitus are described in the SPC Sections 4.4, 4.5 and PIL Sections 2, 4 and appropriate advice is provided to the prescriber to minimise these risks.	None
Use in patients with electrolyte imbalance	The risks associated with the use of the drug product in patients with electrolyte imbalance are described in the SPC Section 4.4 and PIL Section 2 and appropriate advice is provided to the prescriber to minimise these risks.	None
Haematological disorders including anaemia	The risks (1) associated with the use of the drug product in patients with anaemia and (2) of haematological disorders, including anaemia, associated with the use of the drug product are described in the SPC Sections 4.4, 4.8 and PIL Sections 2, 4 and appropriate advice is provided to the prescriber to minimise these risks.	None
Use in patients with debilitating conditions	The risks associated with the use of the drug product in patients with debilitating conditions are	None

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
	described in the SPC Sections 4.4, 4.8 and PIL Sections 2, 4 and appropriate advice is provided to the prescriber to minimise these risks.	
Use in patients with vitamin B (particularly folate) deficiency	The risks associated with the use of the drug product in patients with vitamin B (particularly folate) deficiency are described in the SPC Section 4.4 and PIL Section 2 and appropriate advice is provided to the prescriber to minimise these risks.	None
Gastrointestinal disturbances	The risks (1) of gastrointestinal disturbances associated with the use of the drug product, and (2) associated with the concomitant use of other medicinal products affecting the absorption of the drug product are described in the SPC Sections 4.4, 4.5, 4.8 and PIL Sections 2, 4 and appropriate advice is provided to the prescriber to minimise these risks.	None
Concomitant use with quinolone anti-infectives and typhoid vaccine	The risks associated with concomitant use of the drug product with quinolone anti-infectives and typhoid vaccine are described in the SPC Section 4.5 and PIL Section 2and appropriate advice is provided to the prescriber to minimise these risks.	None
Effect on ability to drive and use machines	The risks of effect on ability to drive and use machines associated with the use of the drug product is described in the SPC Section 4.7 and PIL Sections 2, 4 and appropriate advice is provided to the prescriber to minimise these risks.	None
Important potential risks		

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
None		
Missing information		
None		

VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

A urinary tract infection (UTI) develops when a part of the urinary tract: comprising of kidneys, ureters (tubes carrying urine from kidney to the bladder [where urine is stored]), and urethra (the tube that carries urine from the bladder to the area where it leaves the body) becomes infected, usually by bacteria. The majority of UTIs are caused by three bacteria: *Escherichia coli, Staphylococcus saprophyticus, and Proteus mirabilis,* and cause pain or burning sensation while urinating. The UTIs are much more common in women than men, and affect around 1 in 5 adult women at some point. Among new-borns, boys are slightly at higher risk than girls to present with UTI. In preschool-aged children, the occurrence is approximately 2 in 100 and is 10 times more common in girls. UTI occurs in around 5 per 100 school-aged girls, but it is rare in school-aged boys. [1, 2]

VI.2.2 Summary of treatment benefits

Trimethoprim (an anti-bacterial medicine) or nitrofurantoin remains the drug of choice for the treatment of UTI. About10-20% of bacterial (*E. coli*) UTIs may be resistant (the bacteria which are not killed by the treatment offered). Current recommendations suggest that the treatment period should be no longer than three days in women with UTI, although should remain seven days for the treatment of UTI in men. The first-line therapy in mild cases is an oral fluoroquinolone for seven to ten days. [3, 4]

Nitrofurantoin has been found to be effective in the treatment of UTIs with lesser side-effects as compared to co-trimoxazole and trimethoprim (anti-bacterial medicines). It has been shown as an effective therapy for the treatment of UTI in women. Nitrofurantoin should not be taken by patients who have kidney problem with kidney test of eGFR of less than 45 ml/minute. Nitrofurantoin may be taken only for short duration for treatment of uncomplicated infection of lower urinary system by organisms which are not affected by other medicines and in which in patients who have kidney test of eGFR between 30-44 ml/min, when benefits of using medicine outweigh the risks.

VI.2.3 Unknowns relating to treatment benefits

The true level of resistance in bacteria causing acute UTI in general practice still needs to be addressed, as this will allow better selection of sensitive antibiotics for UTI treatment.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
Allergic reactions (Hypersensitivity)	Use of nitrofurantoin containing medicinal products in patients allergic to nitrofurantoin and other similar medicines can lead to allergic reactions. Use of nitrofurantoin in patients with history of allergic reactions can mask the side-effects of the medicinal product. The allergic reactions may include swelling in the whole body (like lips, eyelids, mouth etc.), rashes associated with redness and itching, fever, and pain in the joints. The patient may also experience difficulty in breathing. Severe skin reactions including Exfoliative dermatitis and erythema multiforme (including life-threatening skin reaction called, Stevens-Johnson Syndrome, characterised by skin loss) have been reported rarely. These conditions are characterised by skin lesions along-with peeling of the skin.	Nitrofurantoin containing medicinal products should not be used in the patients allergic to nitrofurantoin or similar medicines. Nitrofurantoin containing medicinal products should be used with caution in the patients with a history of allergic reactions. If any of severe skin reactions are observed, Nitrofurantoin containing medicinal product should be discontinued immediately and the doctor should be contacted.
Use in patients with kidney impairment (Use in patients with renal impairment)	Nitrofurantoin is ineffective in the treatment of deep kidney infections. Nitrofurantoin is mainly removed from the body by kidneys. When the function of kidneys is compromised, the nitrofurantoin removal process is limited and may increase the levels of nitrofurantoin in blood. Thus, chances of its harmful effects are increased. Creatinine clearance is a test to judge the kidney's capability/function of filtering out the waste products (like creatinine) from blood in urine. Nitrofurantoin may be taken only for short duration for treatment of uncomplicated	Nitrofurantoin containing medicinal products should not be given for the treatment of deep kidney infections. Nitrofurantoin should not be taken by patients who have kidney problem with kidney test of eGFR of less than 45 ml/minute. It should not be used in the elders with kidney function impairment. Simultaneous use of nitrofurantoin containing medicinal products with probenecid, sulphinpyrazone and carbonic anhydrase inhibitors should be avoided.

Risk	What is known	Preventability
	infection of lower urinary system by organisms which are not affected by other medicines and in patients who have kidney test of eGFR between 30-44 ml/min, when benefits of using medicine outweigh the risks. Probenecid and sulphinpyrazone (medicines used to treat pain and swelling in the joints) are removed via kidneys and thus, can interfere with the excretion of nitrofurantoin, leading to its increased concentration and risk of side-effects. Nitrofurantoin requires the acidic environment for its anti-bacterial activity. Thus, decreased acid content by use of carbonic anhydrase inhibitors (medicines used to treat raised pressure in the eyes) and urine alkalinisation (a process whereby urine is made alkaline/less acidic by use of water-pills or sodium bicarbonate) may lead to decreased activity of nitrofurantoin.	
Use in pregnant and breast-feeding women (Use in pregnancy and lactation)	Red blood cells (RBCs) are type of blood cells that provide oxygen to the body tissues. Normally, RBCs last for about 120 days before the body gets rid of them. In haemolytic anaemia, RBCs in the blood are destroyed earlier than normal. The proteins that are responsible for production of RBCs are immature in the unborn child. Thus, nitrofurantoin may cause haemolytic anaemia in the foetus (an unborn child in the womb), if used during labour or delivery. Nitrofurantoin is secreted in the mother’s milk in small amounts and thus, breast-feeding a	Nitrofurantoin containing medicinal products should not be used in pregnant women during labour and delivery. Use of the medicinal product should be avoided in breast-feeding women.

Risk	What is known	Preventability
	new-born baby can be harmful, especially in babies with immature RBCs.	
Use in new-born babies (Use in neonates, less than three months of age)	Nitrofurantoin may cause haemolytic anaemia in the new-born babies, under three months of age due to immature systems involved in the production of RBCs.	Nitrofurantoin containing medicinal products should not be used in babies less than three months of age.
Use in patients with deficiency of an enzyme, glucose-6 phosphate dehydrogenase (Use in patients with glucose-6 phosphate dehydrogenase deficiency)	Glucose-6-phosphate dehydrogenase (G6PD) is an enzyme, which helps the RBCs to function properly. G6PD deficiency results in reduced glutathione (an antioxidant that prevents damage to the RBCs) making the red cells susceptible to damage. Treatment of G6PD-deficient patients with nitrofurantoin causes RBCs to be more easily damaged (this is more common in black people and people of Mediterranean, Middle Eastern, or Asian origin). G6PD deficiency has also been reported with the use of nitrofurantoin.	Nitrofurantoin containing medicinal products should not be used in patients deficient in an enzyme called G6PD (including pregnant women, women who are breast-feeding G6PD-deficient new-born babies, and G6PD-deficient new-born babies) Nitrofurantoin containing medicinal products should be discontinued at any sign of RBCs damage in those with suspected G6PD deficiency.
Use in patients with a genetic disorder affecting blood cell production (Use in patients with acute porphyria)	Acute porphyria is a genetic disorder affecting the production of heme. Heme is an iron-containing compound present throughout the body, especially in the blood and bone marrow, and is responsible for the vital function of oxygen transport. The patients with porphyria disease show overproduction and accumulation of porphyrins in the body due to a lack of controlling enzymes that are involved in the production of red blood cells. High levels of porphyrins commonly cause skin problems, abdominal pain,	Nitrofurantoin containing medicinal products should not be used in patients with acute porphyria.

Risk	What is known	Preventability
	and/or brain-related problems. Nitrofurantoin may cause decreased blood cell count and thus, its use can worsen the condition of the patients with acute porphyria.	
Lung-related problems (Pulmonary disorders)	Use of nitrofurantoin may lead to various lung problems, which may develop quickly, within a week of starting treatment or very slowly, especially in elderly patients. Nitrofurantoin may cause fever, chills, cough, chest pain, shortness of breath, and swelling in the lungs with increased blood cells. Scarring and severe swelling in the lungs have been reported rarely in the patients taking nitrofurantoin for a long-term. On rare occasions, the patient might turn blue in colour (due to shortness of breath) and collapse. Lung functions may be impaired permanently.	If any harmful effect on lungs is noticed, nitrofurantoin containing medicinal products should be discontinued immediately. Since pre-existing lung-related problems may mask the side-effects of nitrofurantoin, the medicinal product should be used with caution in patients with lung-related problems. The doctor should regularly check the lung functions in case of long-term use of the nitrofurantoin containing medicinal products (especially in the elderly).
Liver problems (Hepatic impairments)	Jaundice (inflammation/swelling of the liver causing yellowing of the skin or whites of the eyes) is reported as one of the side-effects related to short-term therapy (usually up to two weeks) of nitrofurantoin. Hepatitis is swelling and inflammation of the liver which usually occurs due to a viral infection. It may start and get better quickly (acute hepatitis), or cause long-term disease (chronic hepatitis). In some instances, it may be associated with severe liver damage. Hepatitis leading to liver damage is generally associated with long-term therapy (usually after six months) of nitrofurantoin.	If any harmful effect on liver is noticed, the nitrofurantoin containing medicinal products should be discontinued immediately. Since pre-existing liver- related problems may mask the side-effects of nitrofurantoin containing medicinal products, it should be used with caution in patients with liver-related problems. The doctor should regularly check the liver functions (especially inflammation of liver) if the patient is taking nitrofurantoin containing medicinal products for a number of months. Due to less effectiveness of the birth-control pills, the patients

Risk	What is known	Preventability
	Nitrofurantoin may reduce the effectiveness of birth-control pills by decreasing its absorption in the body.	taking nitrofurantoin containing medicinal products should use extra precautions like condoms.
Nerves and brain-related disorders (Peripheral neuropathy and neurological disorders)	Peripheral neuropathy describes damage to the peripheral nerves that transmit information from the brain and spinal cord (the central nervous system) to every other part of the body. They also send sensory information back to the brain and spinal cord, such as a message that the feet are cold or a finger is burned. Damage to the peripheral nerves interferes with these vital functions. Use of nitrofurantoin affects the nerves outside the spinal cord which may cause changes to the sense of feeling and the use of muscles. These effects may be severe and in some instances permanent. In addition, headache, extreme changes of mood or mental state, confusion, weakness, spinning feeling, weakness, drowsiness and blurred vision may also occur. Use of nitrofurantoin in patients who are susceptible to peripheral neuropathy and who already have some brain-related disorders may further worsen their condition.	If any harmful effect on nerves or brain-related functions is noticed (explained or unexplained), nitrofurantoin containing medicinal products should be discontinued immediately. Since pre-existing nerves and brain- related problems may mask the side-effects of nitrofurantoin containing medicinal products, therefore it should be used with caution in patients with nerves and brain-related disorders.
Use in patients with high blood sugar (Use in patients with diabetes mellitus)	Diabetes mellitus is a disease in which the blood glucose, or the blood sugar, levels are too high. Use of nitrofurantoin in these patients may further worsen their condition. Nitrofurantoin may interfere with urine tests for glucose, causing the test to give a ‘false-positive’ result, e.g. the test may say that glucose is	Caution should be exercised while using the nitrofurantoin containing medicinal products in patients with diabetes. The patients taking the nitrofurantoin containing medicinal products should inform their doctor before undergoing any urine test for glucose.

Risk	What is known	Preventability
	present in the urine, even if it is not.	
Use in patients with disturbances of salts in blood (Use in patients with electrolyte imbalance)	Electrolytes are minerals (salts) in the body that have an electric charge. Balance of electrolytes is essential for the maintenance of the body functions. Sodium, calcium, potassium, chlorine, phosphate, and magnesium are the electrolytes. Problems most often occur with a change in the levels of sodium, potassium, or calcium. In patients with conditions wherein electrolyte imbalance is observed, use of nitrofurantoin may further worsen their condition.	Caution should be exercised while using nitrofurantoin containing medicinal products in patients with disturbances of salts in blood.
Altered blood cells count (Haematological disorders including anaemia)	In anaemia, the blood does not carry enough oxygen to the rest of the body. The most common cause of anaemia is not having enough iron. The body needs iron to make haemoglobin. Haemoglobin is an iron-rich protein that gives the red colour to blood. It carries oxygen from the lungs to the rest of the body. Anaemia usually occurs due to blood loss, lack of RBC production, and/or high rates of RBCs destruction. The symptoms include pale skin, weakness, and breathlessness. Various types of anaemia are reported with nitrofurantoin use. These include: • Haemolytic anaemia occurs when the bone marrow is unable to replace RBCs that are being destroyed. • Megaloblastic anaemia is a blood disorder in which there is anaemia with larger than normal RBCs. • Aplastic anaemia occurs	Caution should be exercised while using nitrofurantoin containing medicinal products in patients with anaemia. If any of the blood-related abnormalities occur, the medicinal product should be discontinued.

Risk	What is known	Preventability
	rarely and in this type of anaemia, bone marrow does not make enough new blood cells. In patients with conditions wherein the above-said anaemia types are observed, use of nitrofurantoin may further worsen their condition. Decreased white blood cells (blood cells that protect against the body infections) and decreased platelets (responsible for blood clumping) have also been reported with the use of nitrofurantoin. Discontinuation of therapy generally returns the blood picture to normal	
Use in patients with any illness causing severe weakness (Use in patients with debilitating conditions)	Weakness has been reported as a side-effect with nitrofurantoin use. In patients with any illness that is causing severe weakness, use of nitrofurantoin may worsen their condition.	Caution should be exercised while using nitrofurantoin containing medicinal products in patients with any illness causing severe weakness.
Use in patients with vitamin B (particularly folate) deficiency	Vitamins are essential for body functions such as energy production and making RBCs. Folate is one of the vitamins needed to form RBCs. Deficiency of vitamins may compromise these body functions, and further use of nitrofurantoin in these patients may worsen their conditions.	Caution should be exercised while using nitrofurantoin containing medicinal products in patients with vitamin B (particularly folate) deficiency.
Stomach upset (Gastrointestinal disturbances)	Diarrhoea, loss of appetite, stomach pain, and being sick (vomiting) are the side-effects related to the digestive system reported with nitrofurantoin use. Taking nitrofurantoin with food or milk helps to avoid stomach upset and also helps in absorption.	Prolonged-release nitrofurantoin medicinal product (the product which is effective for longer period after single dose) should be taken at meal times with food or milk. Antacids should not be taken simultaneously with nitrofurantoin containing

Risk	What is known	Preventability
	The absorption of nitrofurantoin is increased with food or agents that slow the passage of food through the stomach (like atropine, hyoscine) while magnesium trisilicate (antacid) decreases its absorption.	medicinal products.
Simultaneous use with quinolone anti-infectives and typhoid vaccine (Concomitant use with quinolone anti-infectives and typhoid vaccine)	Quinolone anti-infectives are a class of medicines that is used to treat the bacterial infections. Typhoid vaccine is a special preparation, intended to prevent typhoid disease, caused by a bacteria called *Salmonella typhi*. It contains the live bacteria that has been weakened and works by stimulating the body's defence system against the infection. Quinolone anti-infectives interfere with the action of nitrofurantoin. Also, nitrofurantoin may lead to inactivation of the typhoid vaccine.	The medicinal product should not be used simultaneously with quinolone anti-infectives and typhoid vaccine.
Effects on ability to drive and use machines	Nitrofurantoin has been known to cause dizziness and drowsiness and thus, may interfere with the ability to drive and use machines.	In case the patient experiences dizziness with the medicinal product, he/she should be advised not to drive or operate machinery.

Important potential risks

Risk	What is known
None	

Missing information

Risk	What is known
None	

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

The Summary of Product Characteristics and the Package leaflet for nitrofurantoin can be found in the nitrofurantoin's EPAR page.

No additional risk minimisation measures are planned for this product.

VI.2.6 Planned post-authorisation development plan

Not applicable.

VI.2.7 Summary of changes to the risk management plan over time

This is the first risk management plan for Nitrofurantoin 25 mg/5 mL Oral Suspension, 50 mg/100 mg Tablets and Capsules, and 100 mg Prolonged-Release Capsules.