PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Carbimazole 5mg tablets, Carbimazole 10mg tablets, Carbimazole 15mg tablets, Carbimazole 20mg Tablets, NEOMERCAZOLE 5 mg tablets and NEOMERCAZOLE 20mg tablets (herein referred as Carbimazole).

This is a summary of the risk management plan (RMP) for Carbimazole. The RMP details important risks of Carbimazole, how these risks can be minimised, and how more information will be obtained about Carbimazole's risks and uncertainties (missing information).
Carbimazole's summary of product characteristics (SmPC) and its package leaflet (PIL) give essential information to healthcare professionals and patients on how Carbimazole should be used.

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

I. The medicine and what it is used for

Carbimazole is authorised in all conditions where reduction of thyroid function is required like hyperthyroidism, in preparation for thyroidectomy in hyperthyroidism and as a therapy prior to and post radio-iodine treatment. Carbimazole tablets contain carbimazole as the active substance and are given by oral route.

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

Important risks of Carbimazole, together with measures to minimise such risks and the proposed studies for learning more about Carbimazole'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 the case of Carbimazole, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

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

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

II.A List of important risks and missing information

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

or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Carbimazole. 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);

Summary of safety concerns	
Important identified risks	• Drug induced bone marrow depression including agranulocytosis • Drug induced hepatic injury • Congenital malformations • Acute Pancreatitis
Important potential risks	• None
Missing information	• None

II.B Summary of important risks

Important Identified Risks

Drug induced bone marrow depression including agranulocytosis	
Evidence for linking the risk to the Medicine	Published literature states that drug induced agranulocytosis occurs within 1-2 months of taking the antithyroid medication, but onset delayed by 1½ year. De-challenge resulted normalization of blood parameters. Usually the WBC count returns to normal over a period of 1–2 weeks after discontinuing the offending drug and the time taken can be ranged from 7 to 56 days.[7]
Risk factors and risk groups	• Elderly population • Patients with infection • Patients on medication capable of inducing agranulocytosis Methimazole in higher dose of 30 mg/day age of 40 years or above caused greater risk for development of agranulocytosis.[7]
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC sections 4.2, 4.3, 4.4, 4.5, 4.8 • PIL sections 2, 4 Section 4.2 of the SmPC state care should be taken to observe the contraindications and warnings as it has been reported that the risk of a fatal outcome to neutrophil dyscrasia may be greater in the elderly (aged 65 or over).

	Section 4.3 of the SmPC states that carbimazole is contraindicated in patients with serious, pre-existing haematological conditions. SmPC sections 4.4 and 4.8 provides a warning on bone marrow depression including neutropenia, eosinophilia, leucopenia and agranulocytosis being reported. Section 4.5 of the SmPC also mentions that particular care is required in case of concurrent administration of medication capable of inducing agranulocytosis. **Legal Status:** Prescription-only medicine **Additional risk minimisation measures:** No risk minimisation measures

Drug induced hepatic injury	
Evidence for linking the risk to the Medicine	Published literature states that hepatic injury occurs in less than 1% of patients, with predisposition for younger women (age <30 years). The mechanism of injury is thought to be allergic host response.[8] Hepatic injury induced by these agents could be so severe that might lead to hepatic failure and requirement for liver transplantation.[9]
Risk factors and risk groups	Younger women (age <30 years)
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC sections 4.4, 4.8 • PIL sections 2, 4 Section 4.4 of the SmPC advises that following the onset of any signs and symptoms of hepatic disorder (pain in the upper abdomen, anorexia, general pruritus) in patients, the drug should be stopped and liver function tests performed immediately. Early withdrawal of the drug will increase the chance of complete recovery. SmPC Section 4.8 states that hepatic disorders, including abnormal liver function tests, hepatitis, cholestatic hepatitis, cholestatic jaundice and most commonly jaundice, have been reported and carbimazole tablets should be withdrawn in these cases. **Legal Status:** Prescription-only medicine **Additional risk minimisation measures:** No risk minimisation measures

Congenital malformations	
Evidence for linking the risk to the Medicine	New review of available evidence from epidemiological studies and case reports strengthens the evidence that carbimazole/thiamazole is suspected to cause congenital malformations when administered during pregnancy, particularly in the first trimester of pregnancy and at high doses. The use of carbimazole/thiamazole during pregnancy should be preserved for the situations in which a definitive therapy of the underlying disease (thyroidectomy or radioiodine treatment) was not suitable prior to pregnancy and in case of new occurrence or reoccurrence during pregnancy.[10] An association between the use of ATD in early pregnancy and birth defects was first reported in 1972. An important aspect in the early pregnancy is that the predominant side effect to the use of ATDs in weeks 6–10 of pregnancy is birth defects that may develop after exposure to available types of ATDs and may be severe. In recent years, the risk of birth defects evident from case reports has been corroborated in large clinic- and population-based studies. Studies from Japan and Denmark both reported an increased risk of birth defects in children exposed to MMI/CMZ.[11] Fetal abnormalities are more common in the offspring of women receiving thyroxine and carbimazole (9.5%) than in those treated with carbimazole alone (4.1%).[12] A recent case control study that included over 18 000 cases with congenital malformations, 127 of whom were exposed to anti-thyroid drugs in the first trimester, showed a significant association between *in utero* exposure of carbimazole/methimazole and choanal atresia or omphalocele.[14]
Risk factors and risk groups	Pregnancy and women of childbearing potential
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC section 4.4, 4.6, 4.8 • PIL sections 2, 4 Section 4.4 and 4.6 of the SmPC states that women of childbearing potential have to use effective contraceptive measures during treatment and that the use of carbimazole in pregnant women must be based on the individual benefit/risk assessment. Carbimazole must only be administered during pregnancy after a strict individual benefit/risk assessment and the lowest effective dose without additional administration of thyroid hormones should be administered. Close maternal, foetal and neonatal monitoring is warranted. SmPC Section 4.8 states a causal relationship of these malformations, especially choanal atresia and aplasia cutis congenita (congenital scalp defects), to transplacental exposure to carbimazole and methimazole

	cannot be excluded. Cases of renal, skull, cardiovascular congenital defects, exomphalos, gastrointestinal malformation, umbilical malformation and duodenal atresia have also been reported. **Legal Status:** Prescription-only medicine **Additional risk minimisation measures:** The DHPCs circulated aim to provide the HCPs with important information about the important new risks and measures that will help minimise or prevent these risks.

Acute Pancreatitis	
Evidence for linking the risk to the Medicine	Immediate discontinuation of medicinal products containing carbimazole/thiamazole is required in patients who develop acute pancreatitis following exposure to carbimazole or thiamazole. Carbimazole/thiamazole must not be restarted and affected patients should be switched to an alternative therapy on the basis of the individual benefit/risk assessment. Any future re-exposure to carbimazole/thiamazole in patients who have experienced acute pancreatitis with carbimazole or thiamazole in the past must be avoided, since it may result in recurrence of potentially life-threatening acute pancreatitis, with decreased time to onset.[10]
Risk factors and risk groups	Patients with a history of acute pancreatitis that occurred following administration of carbimazole/thiamazole.
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC section 4.3, 4.4, 4.8 • PIL sections 2, 4 SmPC Section 4.3 contradicts the use of Carbimazole or its active metabolite thiamazole in patients with a history of acute pancreatitis. Section 4.4 of the SmPC warns that in case of acute pancreatitis, carbimazole should be discontinued immediately. Carbimazole must not be given to patients with a history of acute pancreatitis after administration of carbimazole or its active metabolite thiamazole. Re-exposure may result in recurrence of acute pancreatitis, with decreased time to onset. SmPC Section 4.8 reports acute pancreatitis with an unknown frequency. **Legal Status:** Prescription-only medicine **Additional risk minimisation measures:** The DHPCs circulated aim to provide the HCPs with important information about the important new risks and measures that will help minimise or prevent these risks.

Important potential risks

None

Missing information

None

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 for Carbimazole 5mg, 10mg, 15mg and 20mg Tablets.

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

There are no studies required for Carbimazole 5mg, 10mg,15mg and 20mg Tablets.