

**CARBIMAZOLE 5MG TABLETS  
(CARBIMAZOLE)  
PL 20620/0005**

**CARBIMAZOLE 20MG TABLETS  
(CARBIMAZOLE)  
PL 20620/0006**

**UK Public Assessment Report**

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**CARBIMAZOLE 5MG TABLETS**  
**(CARBIMAZOLE)**  
**PL 20620/0005**

**CARBIMAZOLE 20MG TABLETS**  
**(CARBIMAZOLE)**  
**PL 20620/0006**

**LAY SUMMARY**

The Medicines and Healthcare products Regulatory Agency (MHRA) granted NRIM Limited Marketing Authorisations (licences) for the medicinal products Carbimazole 5mg Tablets (PL 20620/0005) and Carbimazole 20mg Tablets (PL 20620/0006) on 18<sup>th</sup> February 2008. These are prescription-only medicines (POM) used for the treatment of thyroid conditions, including hyperthyroidism, where the reduction of thyroid function is required.

These medicinal products contain the active ingredient carbimazole, which belongs to a group of medicines called anti-thyroid agents.

The test products were considered to be the same as the reference products NeoMercazole 5 and NeoMercazole 20 (PL 20072/0013 & 20072/0014, Amdipharm plc) based on the data submitted by NRIM Limited.

These applications are based on reference products with valid UK licences. No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Carbimazole 5mg Tablets and Carbimazole 20mg Tablets outweigh the risks; hence Marketing Authorisations (MAs) have been granted.

**CARBIMAZOLE 5MG TABLETS  
(CARBIMAZOLE)  
PL 20620/0005**

**CARBIMAZOLE 20MG TABLETS  
(CARBIMAZOLE)  
PL 20620/0006**

**SCIENTIFIC DISCUSSION**

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## **INTRODUCTION**

Based on the review of the data on quality, safety and efficacy, the MHRA granted NRIM Limited Marketing Authorisations for the medicinal products Carbimazole 5mg Tablets (PL 20620/0005) and Carbimazole 20mg Tablets (PL 20620/0006) on 18<sup>th</sup> February 2008. The products are prescription-only medicines.

These are abridged applications for Carbimazole 5mg Tablets and Carbimazole 20mg Tablets. These are two strengths of carbimazole, submitted under Article 10.1 of Directive 2001/83/EC, as amended, claiming to be generic medicinal products of the reference products NeoMercazole 5 and NeoMercazole 20 (PL 20072/0013 & 20072/0014) respectively, granted to Amdipharm plc on 31/05/2004. PLs 20072/0013 and 20072/0014 were Change of Ownership applications (CoA) from PL 00031/0378 and PL 00031/0379, which were authorised to Roche Products Limited on 15/09/1987 and 20/06/1986 respectively. These were the innovator products. The reference products have been authorised in the UK for more than 10 years, so the period of data exclusivity has expired.

Carbimazole 5mg Tablets and Carbimazole 20mg Tablets contain the active ingredient carbimazole, which is a thyroid reducing agent. The products are indicated in conditions where reduction of thyroid function is required, including, hyperthyroidism, preparation for thyroidectomy in hyperthyroidism, and preparation for, and as concomitant therapy with, radio-iodine treatment.

These applications for Carbimazole 5mg Tablets and Carbimazole 20mg Tablets were submitted at the same time and both depend on the bioequivalence study presented comparing the applicant's 20mg product with the reference product NeoMercazole 20, manufactured by Roche Products Limited. Consequently, all sections of the Scientific Discussion refer to both products.

## PHARMACEUTICAL ASSESSMENT

### ACTIVE SUBSTANCE

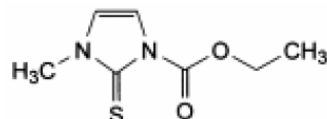
#### Carbimazole

Nomenclature:

INN: Carbimazole

Chemical name: Ethyl 3-methyl-2-thioxo-2,3-dihydro-1*H*-imidazole-1-carboxylate

Structure:



Molecular formula: C<sub>7</sub>H<sub>10</sub>N<sub>2</sub>O<sub>2</sub>S

Molecular weight: 186.2

CAS No: 22232-54-8

Physical form: White to yellowish-white crystalline powder

Solubility: Carbimazole is slightly soluble in water, soluble in acetone and in alcohol

The active substance, carbimazole, is the subject of a European Pharmacopoeia (EP) monograph.

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Confirmation has been provided that the raw materials, intermediates and auxiliary agents used in synthesis of the active are not of animal, biological or genetically modified origin, and therefore comply with the TSE requirements.

An appropriate active substance specification has been provided which is in line with the EP monograph specification. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for reference standards used by the active substance manufacturer during validation studies.

Active carbimazole is stored in appropriate packaging. It is packed, typically 25 or 50 kg, into double polythene bags as the primary container, secured with tamper evident liner ties. The bags are then placed inside fibreboard drums as the secondary container, to which security seals are attached. Specifications and Certificates of Analysis have been provided for the packaging materials used. The polythene bags in direct contact with the active substance satisfy Directive 2002/72/EC (as amended), and are suitable for contact with foodstuffs.

Appropriate stability data have been generated for active substance stored in the proposed packaging. This data demonstrates the stability of the active substance and supports a retest period of 4 years when stored in the proposed packaging.

## **DRUG PRODUCT**

### **Description and Composition**

Carbimazole 5 mg Tablets are white, round, biconvex, uncoated tablets with a score line on one side and embossed 'F1' on the other, whilst Carbimazole 20 mg Tablets are white, round, biconvex, uncoated tablets with a score line on one side and plain on the other.

Other ingredients consist of pharmaceutical excipients, namely lactose monohydrate, maize starch, citric acid monohydrate; and magnesium stearate. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients.

The magnesium stearate is of vegetable origin. The only excipient used that contains material of animal or human origin is lactose monohydrate. A signed TSE / BSE risk-free declaration has been provided by the manufacturer of lactose monohydrate and is acceptable.

There were no novel excipients used and no overages.

### **Dissolution and impurity profiles**

Dissolution profiles for the drug products were found to be similar to those for the reference products, and were satisfactory.

Impurity profiles for the drug products were found to be similar to those for the reference products, and all the impurities are within the specification limits.

### **Pharmaceutical development**

Details of the pharmaceutical development of the drug products have been supplied and are satisfactory.

### **Manufacture**

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation studies have been conducted and are satisfactory.

### **Finished product specification**

The finished product specifications proposed for both release and shelf life are acceptable, and provide an assurance of the quality and consistency of the finished products. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any reference standards used.

### **Container Closure System**

The tablets are presented in polypropylene bottles with child-resistant cap in a pack size of 100 tablets. The specification for the container, Certificate of Analysis and analytical methods have been submitted by the finished product manufacturer and found to be satisfactory. The container complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

### **Stability**

Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 36 months has been set, which is satisfactory. Storage conditions are 'Do not store above 25°C', 'Store in the original container', and 'Keep the container tightly closed'.

### **Bioequivalence Study**

A bioequivalence study was presented comparing the test product, Carbimazole 20mg Tablets, to the reference product, NeoMercazole 20 (manufactured by Roche Products Limited).

An evaluation of the bioequivalence study is found in the Clinical Assessment section.

### **Expert Report**

A satisfactory expert report is provided, and has been prepared by an appropriately qualified expert. An appropriate CV for the expert has been supplied.

### **Product Information**

The approved SmPCs, leaflet, and labelling are satisfactory.

### **Conclusion**

The test products are pharmaceutically equivalent to the reference products which have been licensed in the UK for over 10 years. The drug products correspond to the current EU definition of a generic medicinal product because they comply with the criteria of having the same qualitative and quantitative composition in terms of the active substance and pharmaceutical form. On this basis, and considering the bioequivalence data provided, the applicant's claim that Carbimazole 20mg Tablets is a generic medicinal product of NeoMercazole 20 appears justified.

As the test products, Carbimazole 5mg Tablets and Carbimazole 20mg Tablets, meet the criteria specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence studies on the 20mg strength were extrapolated to the 5mg strength tablets.

All pharmaceutical issues have been resolved and the quality grounds for these applications are considered adequate. It is recommended that Marketing Authorisations are granted.

## **PRECLINICAL ASSESSMENT**

These abridged applications for Carbimazole 5mg Tablets and Carbimazole 2mg Tablets were submitted according to Article 10.1 of Directive 2001/83/EC, as amended.

No new preclinical data have been supplied with these applications and none are required for applications of this type. A preclinical expert report has been written by a suitably qualified person and is satisfactory.



## **CLINICAL ASSESSMENT**

### **INDICATIONS**

Carbimazole 5mg Tablets and Carbimazole 20mg Tablets are indicated in conditions where reduction of thyroid function is required, including hyperthyroidism, preparation for thyroidectomy in hyperthyroidism, and preparation for, and as concomitant therapy with, radio-iodine treatment.

The indications are consistent with those for the innovator product and are satisfactory.

### **POSODOLOGY AND METHOD OF ADMINISTRATION**

The posology is consistent with that for the innovator product and is satisfactory.

### **TOXICOLOGY**

No new data has been submitted and none are required for applications of this type.

### **CLINICAL PHARMACOLOGY**

#### **Pharmacodynamics**

Carbimazole is a thyroid reducing agent.

#### **Pharmacokinetics**

Carbimazole is rapidly metabolised to methimazole. The mean peak plasma concentration of methimazole is reported to occur one hour after a single dose of carbimazole. The apparent plasma half-life of methimazole is reported as 6.4 hours.

#### **Pharmacokinetics - Bioequivalence study**

The applicant presented a single bioequivalence study comparing the test product, Carbimazole 20 mg Tablets, to the reference product, NeoMercazole 20 (Roche Products Limited) under fasting conditions. This was a randomised, single-dose, open-label, crossover, two-treatment, two-period study conducted in 34 healthy adult male subjects.

Treatment periods 1 and 2 were separated by 9 days for wash out purposes. A total of 16 blood samples were collected at regular intervals up to 24 hours post dosing, which was adequate to cover  $AUC_{0-\infty}$ . Plasma samples were analysed employing a validated LC-MS/MS method using MS/MS detection. The pharmacokinetics results were analysed. The rate and extent of absorption of carbimazole were determined by analysing the plasma levels of its metabolite, methimazole, using the primary ( $AUC_{0-24}$ ,  $AUC_{0-\infty}$  and  $C_{max}$ ) and secondary variables ( $T_{max}$ ,  $t_{1/2}$  and  $k_{el}$ ).

The results of the main pharmacokinetic parameters are summarised below.

Pharmacokinetic results of Methimazole for a randomised single dose crossover study between the test and reference product. Log transformed. ANOVA. N = 34 healthy adult male subjects, dosed fasted; t=24 hours. 9 day wash out period

Test parameter	Test product (geometric mean)	Reference product (geometric mean)	Ratio Test/reference x 100	90% Confidence intervals
AUC <sub>0-24</sub> (ng.h/ml)	2097.07	1964.11	106.77	102.90-110.79
AUC <sub>0-∞</sub> (ng.h/ml)	2319.44	2160.97	107.33	103.37-111.45
C <sub>max</sub> (ng/ml)	244.90	225.16	108.77	104.71-112.98
K <sub>el</sub> (h <sup>-1</sup> ) *	0.10	0.10	-	-
T <sub>1/2</sub> (h) *	6.82	6.74	-	-
T <sub>max</sub> (h) *	0.95	1.40	-	-

\* Arithmetic values

The 90% confidence intervals for the log-transformed parameters C<sub>max</sub>, AUC<sub>0-t</sub> and AUC<sub>0-∞</sub> of Methimazole lie within the range 80-125%, such that the test and reference products can be considered bioequivalent after a single dose under fasted conditions.

As Carbimazole 5mg Tablets and Carbimazole 20mg Tablets meet the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 20mg strength were extrapolated to the 5mg strength product.

## EFFICACY

No new data are submitted and none are required for applications of this type.

Efficacy is reviewed in the Clinical Expert Report. The reference products are established and the applications depend upon the bioequivalence study.

## SAFETY

No new data are submitted and none are required for applications of this type.

Safety is reviewed in the Clinical Expert Report. The reference products are established and the applications depend upon the bioequivalence study.

## EXPERT REPORT

A satisfactory expert report is provided, and has been prepared by an appropriately qualified expert. An appropriate CV for the expert has been supplied.

## PRODUCT INFORMATION:

### Summary of Product Characteristics (SmPC)

The approved SmPCs are consistent with those for the reference products and are acceptable.

### Patient Information Leaflet (PIL)

The PIL is in line with the approved SmPCs and is satisfactory.

**Labelling**

Colour mock-ups of the labelling have been provided. The labelling is satisfactory and fulfils the statutory requirements for Braille.

**CONCLUSIONS**

All issues have been adequately addressed by the applicant. The bioequivalence study was of an appropriate design and demonstrates the bioequivalence of the test (Carbimazole 20mg Tablets) and reference (NeoMercazole 20) products within general acceptance limits. The results and conclusions of the bioequivalence study on the 20mg strength were extrapolated to the 5mg strength product. Therefore, the 5mg strength carbimazole formulation is bioequivalent to its corresponding marketed brand formulation, despite bioequivalence not being assessed explicitly.

Sufficient clinical information has been submitted to support these applications. Marketing Authorisations may be granted on medical grounds.

## **OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT**

### **QUALITY**

The important quality characteristics of Carbimazole 5mg Tablets and Carbimazole 20mg Tablets are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

### **PRECLINICAL**

No new preclinical data were submitted and none are required for applications of this type.

### **EFFICACY**

Bioequivalence has been demonstrated between the applicant's Carbimazole 20mg Tablets, and the reference product NeoMercazole 20 (Amdipharm plc). As the applicant's products were deemed to meet the criteria specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 20mg strength were extrapolated to the 5mg tablet strength. Thus, no separate bioequivalence studies were necessary for this strength.

No new or unexpected safety concerns arise from these applications.

### **PRODUCT LITERATURE**

The SmPCs, PIL and labelling are satisfactory and consistent with those for NeoMercazole 5 and NeoMercazole 20.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

The approved labelling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the product label.

### **RISK BENEFIT ASSESSMENT**

The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study, and the valid extrapolation of its results and conclusions, support the claim that the applicant's products and their respective reference products are interchangeable. Extensive clinical experience with carbimazole is considered to have demonstrated the therapeutic value of the active substance. The risk: benefit is, therefore, considered to be positive.

**CARBIMAZOLE 5MG TABLETS**  
**(CARBIMAZOLE)**  
**PL 20620/0005**

**CARBIMAZOLE 20MG TABLETS**  
**(CARBIMAZOLE)**  
**PL 20620/0006**

**STEPS TAKEN FOR ASSESSMENT**

- 1 The MHRA received the marketing authorisation applications on 18<sup>th</sup> May 2005
- 2 Following standard checks and communication with the applicant the MHRA considered the applications valid on 22<sup>nd</sup> June 2005
- 3 Following assessment of the applications the MHRA requested further information relating to the quality dossiers on 6<sup>th</sup> April 2006
- 4 The applicant responded to the MHRA's requests, providing further information for the quality sections on 23<sup>rd</sup> May 2006
- 5 Following assessment of the response the MHRA requested further information relating to the quality sections on 4<sup>th</sup> August 2006, 14<sup>th</sup> August 2006, and 27<sup>th</sup> November 2006
- 6 The applicant responded to the MHRA's requests, providing further information for the quality sections on 9<sup>th</sup> August 2006, 24<sup>th</sup> November 2006, and 22<sup>nd</sup> March 2007 respectively
- 7 The MHRA requested further information relating to the clinical dossier on 9<sup>th</sup> July 2007, and further information relating to the quality sections on 21<sup>st</sup> November 2007
- 8 The applicant responded to the MHRA's requests, providing further information for the clinical and quality sections on 30<sup>th</sup> November 2007
- 9 The applications were determined on 18<sup>th</sup> February 2008

## SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SPC) for Carbimazole 5mg Tablets is as follows:

### 1 NAME OF THE MEDICINAL PRODUCT

Carbimazole 5mg Tablets

### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Carbimazole Ph. Eur. 5mg

Each tablet also contains lactose monohydrate. For full list of excipients, see section 6.1

### 3 PHARMACEUTICAL FORM

Tablet - White, round, biconvex, uncoated tablets with a score line on one side and embossed 'F1' on the other

### 4 CLINICAL PARTICULARS

#### 4.1 THERAPEUTIC INDICATIONS

Carbimazole is an anti-thyroid agent. It is indicated in all conditions where reduction of thyroid function is required.

1. Hyperthyroidism.
2. Preparation for thyroidectomy in hyperthyroidism.
3. Preparation for, and as concomitant therapy with, radio-iodine treatment.

#### 4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Carbimazole should only be administered if hyperthyroidism has been confirmed by laboratory tests

##### *Adults*

The initial dose is in the range 20 - 60mg and should be titrated against thyroid function until the patient is euthyroid in order to reduce the risk of over-treatment and resultant hypothyroidism. Subsequent therapy may then be administered in one of two ways.

*Maintenance regimen:* Final dosage is usually in the range 5 - 15mg per day, which may be taken as a single daily dose. Therapy should be continued for at least six, and up to 18 months. Serial thyroid function monitoring is recommended, together with appropriate dosage modification in order to maintain a euthyroid state.

*Blocking-replacement regimen:* Dosage is maintained at the initial level, i.e. 20 - 60mg per day, and supplemental l-thyroxine, 50 - 150mcg per day, is administered concomitantly, in order to prevent hypothyroidism. Therapy should be continued for at least six months, and up to eighteen months.

Where a single dosage of less than 20mg is recommended, it is intended that Carbimazole 5mg Tablets should be taken.

##### **ELDERLY**

No special dosage regimen is required, but care should be taken to observe the contra-indications and warnings.

##### *Children*

The usual initial daily dose is 15mg per day.

#### 4.3 CONTRAINDICATIONS

Carbimazole is contra-indicated in patients with a previous history of adverse reactions to carbimazole or to any of the excipients in the composition. Serious, pre-existing haematological conditions, severe hepatic insufficiency.

#### 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

As fatal cases of agranulocytosis with carbimazole have been reported and early treatment of agranulocytosis is essential, it is important that patients should always be warned about the onset of sore throats, bruising or bleeding, mouth ulcers, fever, malaise and should be instructed to stop the drug and to seek medical advice immediately. In such patients, blood cell counts should be performed immediately, particularly where there is any clinical evidence of infection.

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.

Carbimazole should be used with caution in patients with mild-moderate hepatic insufficiency. If abnormal liver function is discovered, the treatment should be stopped. The half-life may be prolonged due to the liver disorder.

Carbimazole should be stopped temporarily at the time of administration of radio-iodine. Patients unable to comply with the instructions for use or who cannot be monitored regularly should not be treated with carbimazole.

Regular full blood count checks should be carried out in patients who may be confused or have a poor memory.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Precaution should be taken in patients with intrathoracic goitre, which may worsen during initial treatment with carbimazole. Tracheal obstruction may occur due to intrathoracic goitre. The use of carbimazole in non-pregnant women of childbearing potential should be based on individual risk/benefit assessment (see section 4.6).

There is a risk of cross-allergy between carbimazole, thiamazole and propylthiouracil.

#### 4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Little is known about interactions.

Particular care is required in case of concurrent administration of medication capable of inducing agranulocytosis. Since carbimazole is a vitamin K antagonist, the effect of anticoagulants could be intensified.

The serum levels of theophylline can increase and toxicity may develop if patients are treated with antithyroid medications without reducing the theophylline dosage.

#### 4.6 PREGNANCY AND LACTATION

Carbimazole crosses the placenta but, provided the mother's dose is within the standard range, and her thyroid status is monitored; there is no evidence of neonatal thyroid abnormalities. Studies have shown that the incidence of congenital malformations is greater in the children of mothers whose hyperthyroidism has remained untreated than in those to whom treatment with carbimazole has been given.

However, very rare cases of congenital malformations have been observed following the use of carbimazole or its active metabolite methimazole during pregnancy. A causal relationship of these malformations, especially choanal atresia and aplasia cutis congenita, to transplacental exposure to carbimazole and methimazole cannot be excluded. Therefore, the use of carbimazole in non-pregnant women of childbearing potential should be based on individual risk/benefit assessment (see section 4.4).

Cases of renal, skull, cardiovascular congenital defects, exomphalos, gastrointestinal malformation, umbilical malformation and duodenal atresia have also been reported. Therefore, carbimazole should be used in pregnancy only when propylthiouracil is not suitable. If carbimazole is used in pregnancy the dose of carbimazole must be regulated by the

patient's clinical condition. The lowest dose possible should be used, and this can often be discontinued three to four weeks before term, in order to reduce the risk of neonatal complications. The blocking-replacement regimen should not be used during pregnancy since very little thyroxine crosses the placenta in the last trimester.

Carbimazole is secreted in breast milk and, if treatment is continued during lactation, the patient should not continue to breast-feed her baby.

#### **4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES**

The effect on the ability to drive and use machines is not known

#### **4.8 UNDESIRABLE EFFECTS**

Adverse reactions usually occur in the first eight weeks of treatment. The most frequently occurring reactions are nausea, headache, arthralgia, mild gastric distress, skin rashes and pruritus. These reactions are usually self-limiting and may not require withdrawal of the drug.

##### ***Blood and lymphatic system disorders***

Bone marrow depression including neutropenia, eosinophilia, leukopenia, and agranulocytosis has been reported. Fatalities with carbimazole-induced agranulocytosis have been reported. Rare cases of pancytopenia/aplastic anaemia and isolated thrombocytopenia have also been reported. Additionally, very rare cases of haemolytic anaemia have been reported.

Patients should always be warned about the onset of sore throats, bruising or bleeding, mouth ulcers, fever, malaise and should be instructed to stop the drug and to seek medical advice immediately. In such patients, blood cell counts should be performed immediately, particularly where there is any clinical evidence of infection.

##### ***NERVOUS SYSTEM DISORDERS***

Headache.

##### ***Gastro-intestinal system disorders***

Nausea, mild gastric distress. Loss of sense of taste has been observed.

##### ***General disorders and administration site conditions***

Fever, Malaise

##### ***Hepato-biliary system disorders***

Hepatic disorders, including abnormal liver function tests, hepatitis, cholestatic hepatitis, cholestatic jaundice and most commonly jaundice, have been reported; in these cases carbimazole should be withdrawn.

##### ***Injury, poisoning and procedural complications***

Bruising

##### ***Skin and subcutaneous tissue disorders***

Skin rashes, pruritus, urticaria. Hair loss has been occasionally reported.

##### ***Musculoskeletal system disorders***

Isolated cases of myopathy have been reported. Patients experiencing myalgia after the intake of carbimazole should have their creatine phosphokinase levels monitored.

##### ***Hypersensitivity and allergic reaction***

Angioedema and multi-system hypersensitivity reactions such as cutaneous vasculitis, liver, lung and renal effects occur.

##### ***Vascular Disorders***

Bleeding

#### **4.9 OVERDOSE**

No symptoms are likely from a single large dose, and so no specific treatment is indicated.



**5 PHARMACOLOGICAL PROPERTIES****5.1 PHARMACODYNAMIC PROPERTIES**

Carbimazole is a thyroid reducing agent. ATC code: H03BB01

**5.2 PHARMACOKINETIC PROPERTIES**

Carbimazole is rapidly metabolised to methimazole. The mean peak plasma concentration of methimazole is reported to occur one hour after a single dose of carbimazole. The apparent plasma half-life of methimazole is reported as 6.4 hours.

**5.3 PRECLINICAL SAFETY DATA**

Not relevant.

**6 PHARMACEUTICAL PARTICULARS****6.1 LIST OF EXCIPIENTS**

Lactose monohydrate  
Maize Starch  
Citric acid monohydrate  
Magnesium stearate

**6.2 INCOMPATIBILITIES**

Not applicable

**6.3 SHELF LIFE**

36 months

**6.4 SPECIAL PRECAUTIONS FOR STORAGE**

Do not store above 25°C. Store in original container. Keep the container tightly closed

**6.5 NATURE AND CONTENTS OF CONTAINER**

Tablets are packed in an PP container with child resistant cap containing 100 tablets.

**6.6 SPECIAL PRECAUTIONS FOR DISPOSAL**

No special requirements.

**7 MARKETING AUTHORISATION HOLDER**

NRIM Limited  
Marlborough House  
298, Regents Park Road  
Finchley N3 2UA  
London, United Kingdom

**8 MARKETING AUTHORISATION NUMBER(S)**

PL 20620/0005

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

18/02/2008

**10 DATE OF REVISION OF THE TEXT**

18/02/2008

## SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SPC) for Carbimazole 20mg Tablets is as follows:

### 1 NAME OF THE MEDICINAL PRODUCT

Carbimazole 20mg Tablets

### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Carbimazole Ph. Eur. 20mg

Each tablet also contains lactose monohydrate. For full list of excipients, see section 6.1

### 3 PHARMACEUTICAL FORM

Tablet - Tablets are white, round, biconvex, uncoated tablets with a score line on one side and plain on the other

### 4 CLINICAL PARTICULARS

#### 4.1 THERAPEUTIC INDICATIONS

Carbimazole is an anti-thyroid agent. It is indicated in all conditions where reduction of thyroid function is required.

1. Hyperthyroidism.
2. Preparation for thyroidectomy in hyperthyroidism.
3. Preparation for, and as concomitant therapy with, radio-iodine treatment.

#### 4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Carbimazole should only be administered if hyperthyroidism has been confirmed by laboratory tests

##### *Adults*

The initial dose is in the range 20 - 60mg and should be titrated against thyroid function until the patient is euthyroid in order to reduce the risk of over-treatment and resultant hypothyroidism. Subsequent therapy may then be administered in one of two ways.

*Maintenance regimen:* Final dosage is usually in the range 5 - 15mg per day, which may be taken as a single daily dose. Therapy should be continued for at least six, and up to 18 months. Serial thyroid function monitoring is recommended, together with appropriate dosage modification in order to maintain a euthyroid state.

*Blocking-replacement regimen:* Dosage is maintained at the initial level, i.e. 20 - 60mg per day, and supplemental l-thyroxine, 50 - 150mcg per day, is administered concomitantly, in order to prevent hypothyroidism. Therapy should be continued for at least six months, and up to eighteen months.

Where a single dosage of less than 20mg is recommended, it is intended that Carbimazole 5mg Tablets should be taken.

##### **ELDERLY**

No special dosage regimen is required, but care should be taken to observe the contra-indications and warnings.

##### *Children*

The usual initial daily dose is 15mg per day.

#### 4.3 CONTRAINDICATIONS

Carbimazole is contra-indicated in patients with a previous history of adverse reactions to carbimazole or to any of the excipients in the composition. Serious, pre-existing haematological conditions, severe hepatic insufficiency.

#### 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

As fatal cases of agranulocytosis with carbimazole have been reported and early treatment of agranulocytosis is essential, it is important that patients should always be warned about the onset of sore throats, bruising or bleeding, mouth ulcers, fever, malaise and should be instructed to stop the drug and to seek medical advice immediately. In such patients, blood cell counts should be performed immediately, particularly where there is any clinical evidence of infection.

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.

Carbimazole should be used with caution in patients with mild-moderate hepatic insufficiency. If abnormal liver function is discovered, the treatment should be stopped. The half-life may be prolonged due to the liver disorder.

Carbimazole should be stopped temporarily at the time of administration of radio-iodine. Patients unable to comply with the instructions for use or who cannot be monitored regularly should not be treated with carbimazole.

Regular full blood count checks should be carried out in patients who may be confused or have a poor memory.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Precaution should be taken in patients with intrathoracic goitre, which may worsen during initial treatment with carbimazole. Tracheal obstruction may occur due to intrathoracic goitre. The use of carbimazole in non-pregnant women of childbearing potential should be based on individual risk/benefit assessment (see section 4.6).

There is a risk of cross-allergy between carbimazole, thiamazole and propylthiouracil.

#### 4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Little is known about interactions.

Particular care is required in case of concurrent administration of medication capable of inducing agranulocytosis. Since carbimazole is a vitamin K antagonist, the effect of anticoagulants could be intensified.

The serum levels of theophylline can increase and toxicity may develop if patients are treated with antithyroid medications without reducing the theophylline dosage.

#### 4.6 PREGNANCY AND LACTATION

Carbimazole crosses the placenta but, provided the mother's dose is within the standard range, and her thyroid status is monitored; there is no evidence of neonatal thyroid abnormalities. Studies have shown that the incidence of congenital malformations is greater in the children of mothers whose hyperthyroidism has remained untreated than in those to whom treatment with carbimazole has been given.

However, very rare cases of congenital malformations have been observed following the use of carbimazole or its active metabolite methimazole during pregnancy. A causal relationship of these malformations, especially choanal atresia and aplasia cutis congenita, to transplacental exposure to carbimazole and methimazole cannot be excluded. Therefore, the use of carbimazole in non-pregnant women of childbearing potential should be based on individual risk/benefit assessment (see section 4.4).

Cases of renal, skull, cardiovascular congenital defects, exomphalos, gastrointestinal malformation, umbilical malformation and duodenal atresia have also been reported. Therefore, carbimazole should be used in pregnancy only when propylthiouracil is not suitable. If carbimazole is used in pregnancy the dose of carbimazole must be regulated by the

patient's clinical condition. The lowest dose possible should be used, and this can often be discontinued three to four weeks before term, in order to reduce the risk of neonatal complications. The blocking-replacement regimen should not be used during pregnancy since very little thyroxine crosses the placenta in the last trimester.

Carbimazole is secreted in breast milk and, if treatment is continued during lactation, the patient should not continue to breast-feed her baby.

#### **4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES**

The effect on the ability to drive and use machines is not known

#### **4.8 UNDESIRABLE EFFECTS**

Adverse reactions usually occur in the first eight weeks of treatment. The most frequently occurring reactions are nausea, headache, arthralgia, mild gastric distress, skin rashes and pruritus. These reactions are usually self-limiting and may not require withdrawal of the drug.

##### ***Blood and lymphatic system disorders***

Bone marrow depression including neutropenia, eosinophilia, leukopenia, and agranulocytosis has been reported. Fatalities with carbimazole-induced agranulocytosis have been reported. Rare cases of pancytopenia/aplastic anaemia and isolated thrombocytopenia have also been reported. Additionally, very rare cases of haemolytic anaemia have been reported.

Patients should always be warned about the onset of sore throats, bruising or bleeding, mouth ulcers, fever, malaise and should be instructed to stop the drug and to seek medical advice immediately. In such patients, blood cell counts should be performed immediately, particularly where there is any clinical evidence of infection.

##### ***NERVOUS SYSTEM DISORDERS***

Headache.

##### ***Gastro-intestinal system disorders***

Nausea, mild gastric distress. Loss of sense of taste has been observed.

##### ***General disorders and administration site conditions***

Fever, Malaise

##### ***Hepato-biliary system disorders***

Hepatic disorders, including abnormal liver function tests, hepatitis, cholestatic hepatitis, cholestatic jaundice and most commonly jaundice, have been reported; in these cases carbimazole should be withdrawn.

##### ***Injury, poisoning and procedural complications***

Bruising

##### ***Skin and subcutaneous tissue disorders***

Skin rashes, pruritus, urticaria. Hair loss has been occasionally reported.

##### ***Musculoskeletal system disorders***

Isolated cases of myopathy have been reported. Patients experiencing myalgia after the intake of carbimazole should have their creatine phosphokinase levels monitored.

##### ***Hypersensitivity and allergic reaction***

Angioedema and multi-system hypersensitivity reactions such as cutaneous vasculitis, liver, lung and renal effects occur.

##### ***Vascular Disorders***

Bleeding

#### **4.9 OVERDOSE**

No symptoms are likely from a single large dose, and so no specific treatment is indicated.

**5 PHARMACOLOGICAL PROPERTIES****5.1 PHARMACODYNAMIC PROPERTIES**

Carbimazole is a thyroid reducing agent. ATC code: H03BB01

**5.2 PHARMACOKINETIC PROPERTIES**

Carbimazole is rapidly metabolised to methimazole. The mean peak plasma concentration of methimazole is reported to occur one hour after a single dose of carbimazole. The apparent plasma half-life of methimazole is reported as 6.4 hours.

**5.3 PRECLINICAL SAFETY DATA**

Not relevant.

**6 PHARMACEUTICAL PARTICULARS****6.1 LIST OF EXCIPIENTS**

Lactose monohydrate  
Maize Starch  
Citric acid monohydrate  
Magnesium stearate

**6.2 INCOMPATIBILITIES**

Not applicable

**6.3 SHELF LIFE**

36 months

**6.4 SPECIAL PRECAUTIONS FOR STORAGE**

Do not store above 25°C. Store in original container. Keep the container tightly closed

**6.5 NATURE AND CONTENTS OF CONTAINER**

Tablets are packed in an PP container with child resistant cap containing 100 tablets.

**6.6 SPECIAL PRECAUTIONS FOR DISPOSAL**

No special requirements.

**7 MARKETING AUTHORISATION HOLDER**

NRIM Limited  
Marlborough House  
298, Regents Park Road  
Finchley N3 2UA  
London, United Kingdom

**8 MARKETING AUTHORISATION NUMBER(S)**

PL 20620/0006

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

18/02/2008

**10 DATE OF REVISION OF THE TEXT**

18/02/2008

## PATIENT INFORMATION LEAFLET



## PACKAGE LEAFLET: INFORMATION FOR THE USER

### CARBIMAZOLE 5MG & 20MG TABLETS

#### READ ALL OF THIS LEAFLET CAREFULLY BEFORE YOU START USING THIS MEDICINE.

- Keep this leaflet. You may need to read it again
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

#### THE LEAFLET CONTAINS INFORMATION ON:

1. What are Carbimazole Tablets and what are they used for.
2. Before you take Carbimazole Tablets
3. How to take Carbimazole Tablets
4. Possible side effects
5. How to store Carbimazole Tablets
6. Further Information

#### 1. WHAT ARE CARBIMAZOLE TABLETS AND WHAT ARE THEY USED FOR?

Carbimazole belongs to a group of medicines called anti-thyroid agents. It is used for the following:

- Hyperthyroidism, which is a condition where in the thyroid gland is hyperactive. Carbimazole is used to reduce the formation of thyroid hormones
- Treatment in more serious cases, for example, to restore the normal function of the thyroid before its partial removal by surgery.
- It is also used together with other treatments for overactive thyroid.

#### 2. BEFORE YOU TAKE CARBIMAZOLE TABLETS

##### Do not take Carbimazole Tablets if:

- You are allergic to carbimazole or any other ingredients in the products.
- You are breast-feeding.
- If you have a serious blood disorder
- If you have a severe liver disorder

##### Take special care with Carbimazole Tablets and consult your doctor:

- If you are pregnant or think that you may be pregnant or are trying to become pregnant.
- If you have mild or moderate liver problems

Your doctor may ask you for occasional blood tests to help him determine how you are responding to treatment

##### Taking other medicine

Please tell your doctor or pharmacist if you are taking or have recently taken other medicines including medicines

obtained without a prescription, or the following:

- Theophylline used to treat asthma or breathing problems
- Medicines called anticoagulants, which are used to thin the blood e.g. warfarin

##### Taking Carbimazole Tablets with food or drink

Carbimazole Tablets may be taken with or without food

##### Pregnancy and breast-feeding

Carbimazole may need to be continued during pregnancy but very rarely it can cause harm to a developing foetus. However, to reduce the possibility of any effects on your baby:

- Your doctor should prescribe the lowest dose possible.
- Your treatment may be discontinued 3 to 4 weeks before you are due to give birth.
- You should not breast feed if you are using Carbimazole.

Ask you doctor or pharmacist for advice before taking any medicine

##### Driving and using machines

The effects of Carbimazole on the ability to drive and operate machinery have not been established. Hence do not drive or use machinery when you are on Carbimazole Tablets unless you are sure your judgement and co-ordination are not affected.

##### Important information about some of the ingredients of Carbimazole Tablets

Carbimazole Tablets contain Lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product

#### 3. HOW TO TAKE CARBIMAZOLE TABLETS

Always take Carbimazole Tablets exactly as your doctor has told you. Do not increase or decrease the dose on your own. You should check with your doctor or pharmacist if you are not sure. The usual starting dose for adults is one to three 20mg tablets or four to twelve 5mg tablets. For children the usual starting dose is three 5mg tablets.

Once control is achieved your doctor will gradually reduce your dose to one to three 5mg tablets each day.

You may be given an additional L-thyroxine tablet, to help control your condition. Each day's tablets may be divided into two or three daily doses.

In order to maintain control of the thyroid gland, you may need to continue to take carbimazole tablets for several

months. Your doctor will decide when treatment can be stopped. He may ask you to have occasional blood tests to help him determine how you are responding to treatment.

Radio-iodine is another treatment for hyperthyroidism. If you need radio-iodine treatment, your doctor will tell you to stop taking carbimazole temporarily.

If you have the impression that the effect of Carbimazole Tablet is too strong or too weak, talk to your doctor or pharmacist.

#### **If you take more Carbimazole Tablets than you should**

It is important to stick to the dose on the label of the medicine. If you or someone else swallows several of these tablets all together, contact your doctor or nearest hospital emergency department immediately. Always take any tablets left over with you and also the box, as this will allow easier identification of the tablets.

#### **If you forget to take Carbimazole Tablets**

If you forget to take a dose, take it as soon as you remember. If it is almost time for your next dose do not take a double dose to make up for a forgotten dose, just carry on as before.

#### **If you stop taking Carbimazole Tablets**

In order to maintain control of the thyroid gland, you may need to continue to take Carbimazole tablets for several months.

#### **4. POSSIBLE SIDE EFFECTS**

Like all medicines, Carbimazole Tablets can have side effects although not everybody gets them.

#### **Stop taking Carbimazole Tablets and tell your doctor immediately if you experience any of the following symptoms:**

- Sore throat
- Mouth ulcers
- High temperature or fever
- Significant tiredness
- Increased bruising or bleeding tendency
- You are feeling generally unwell or think that you may have an infection

Some tests should be performed to check for bone marrow depression before restarting your treatment. Bone marrow depression causes a reduction in the number of blood cells and reduces the ability to fight infection. If it is not treated as soon as it is detected the condition could become life-threatening.

#### **Tell your doctor if:**

You experience muscle aches or pains or notice yellowing of your skin or the whites of your eyes as carbimazole can also affect your muscles or the liver (causing jaundice and inflammation of the liver). Under medical supervision, the drug should be stopped and blood tests performed.

Other side effects include:

- feeling sick
- headache
- skin rashes, including urticaria (nettle rash)
- itching

- stomach upset
- painful joints

The following side effects have also been reported:

- hair loss
- loss of taste
- angioedema, a serious allergic reaction with symptoms that may include swollen tongue, lips, face or throat
- Lung problems, with symptoms that include shortness of breath or cough
- Kidney problems, with symptoms that include a reduction in the amount of urine passed, fluid retention and blood in the urine

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist as soon as possible.

#### **5. HOW TO STORE CARBIMAZOLE TABLETS**

- Keep out of the reach and sight of children.
- Do not use Carbimazole Tablets after the expiry date, which is stated on the label and carton. The expiry date refers to the last day of the month.
- Store your tablets in the original container. Keep the container tightly closed. Do not store above 25°C.
- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

#### **6. FURTHER INFORMATION**

##### **What Carbimazole Tablets contain**

The name of your medicine is Carbimazole 5mg or 20mg Tablets.

The active substance in your tablet is carbimazole. Each tablet contains 5mg or 20mg of carbimazole. Other ingredients are lactose monohydrate, maize starch, citric acid monohydrate and magnesium stearate.

##### **What Carbimazole Tablets look like and contents of the pack**

Carbimazole 5mg Tablets are white, round, biconvex, uncoated tablets with a score line on one side and embossed 'F1' on the other.

Carbimazole 20mg Tablets are white, round, biconvex, uncoated tablets with a score line on one side and plain on the other.

Carbimazole 5mg or 20mg Tablets are supplied in bottles of 100 tablets.

##### **Marketing Authorisation Holder and Manufacturer**

The Marketing Authorisation holder: NRI Limited Marlborough House, 298 Regents Park Road, Finchley, London, N3 2UA, United Kingdom

The tablets are manufactured by: NRI Limited Marlborough House, 298 Regents Park Road, Finchley, London, N3 2UA, United Kingdom

This leaflet was prepared in 01/2008

**LABELLING**

**Carbimazole 5mg Tablets**

Label for bottle, with braille

**CARBIMAZOLE**

**5MG TABLETS**

**100 Tablets**

Tablets for oral administration.  
As prescribed by the physician.  
Each tablet contains Carbimazole 5mg.

Also contains lactose monohydrate.

Do not store above 25 °C. Store in the original container.  
Keep the container tightly closed.  
Store out of the reach and sight of children.


For further information see the attached leaflet.

P.L. Number 20620/0005  
P.L. Holder: NRI Limited, Marlborough House, 298, Regents Park Road, Finchley, London N3 2UA, UK.

5mg

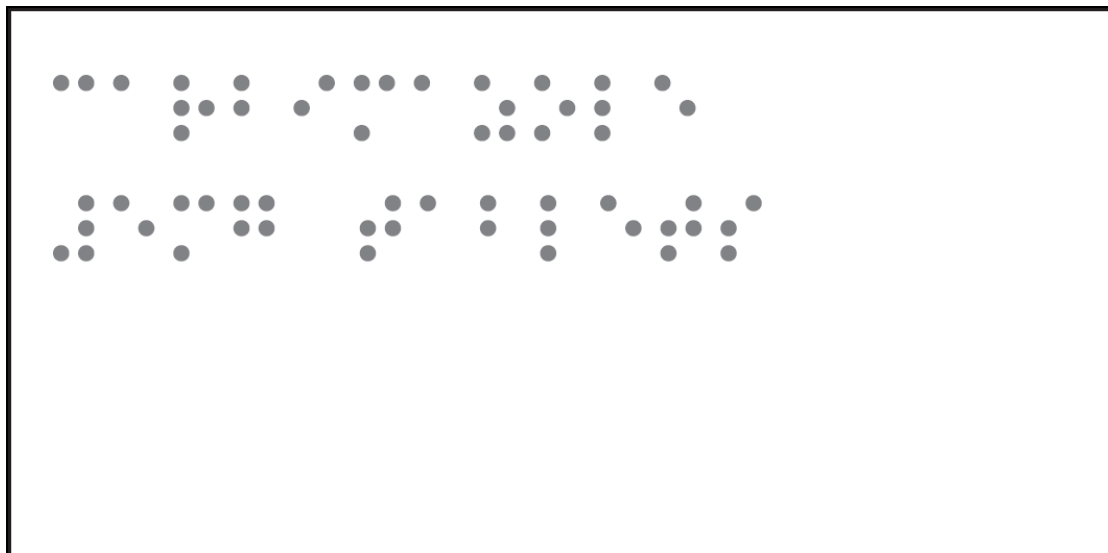
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Braille only





**Carbimazole 20mg Tablets**

Label for bottle, with braille

**CARBIMAZOLE**  
20MG TABLETS  
**100 Tablets**


Tablets for oral administration.  
As prescribed by the physician.  
Each tablet contains Carbimazole 20mg.

Also contains lactose monohydrate.


Do not store above 25 °C. Store in the original container.  
Keep the container tightly closed.  
Store out of the reach and sight of children.

For further information see the attached leaflet.

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Braille only

