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2.5 Clinical Overview

2.5.1. Product Development Rationale

Pharmacotherapeutic group: Sulfur-containing imidazole derivatives.

ATC Code: H03B B01

Non-Proprietary Name of the Drug Product: Carbimazole 10 mg and 15 mg Tablets

Non-Proprietary Name of the Drug Substance: Carbimazole Ph. Eur.

Dosage Form: Tablets

Strength: 10 mg and 15 mg

Route of Administration: Oral

Targeted Indication(s): Carbimazole is an anti-thyroid agent. It is indicated in adults and children in all conditions where reduction of thyroid function is required.[1]

Such conditions are:

- Hyperthyroidism.
- Preparation for thyroidectomy in hyperthyroidism.
- Therapy prior to and post radio-iodine treatment.

Carbimazole, a thionamide, is a pro-drug which undergoes rapid and virtually complete metabolism to the active metabolite, thiamazole, also known as methimazole. The method of action is believed to be inhibition of the organification of iodide and the coupling of iodothyronine residues which in turn suppress the synthesis of thyroid hormones.

Current application for generic products Carbimazole 10 mg and 15 mg Tablets, is submitted under Regulation 52B of The Human Medicines Regulations 2012, as a Hybrid Application [previously Article 10(3) of Directive 2001/83/EC]. This is cross-referred to UK reference product NeoMercazole® 20 mg Tablets, (PL 20072/0014) of MAH- Amdipharm UK Limited, first authorized on 20 June 1986. The reference products for Carbimazole 10 mg and 15 mg Tablets is not available in the UK market.

The ‘ten year rule’ applies and in accordance with these provisions, the applicant has not conducted clinical studies in support of this application.

The test products are immediate release solid dose preparations for oral use with same pharmaceutical form as that of Reference Product NeoMercazole®.

Applicant's proposed lower strengths, Carbimazole 10 mg and 15 mg Tablets, are developed as dose weight proportionate formulations of higher bio-strength Carbimazole 20 mg (which is already granted marketing authorization PL 43461/0035 in the UK).

Subjected application is supported by the bio-waiver request based on the bioequivalence study conducted on higher strength Carbimazole 20 mg tablets as per the 'Guideline on the Investigation of Bioequivalence' (CPMP/QWP/EWP/1401/98 Rev. 1/ Corr**) using European Reference Product NeoMercazole 20 mg Tablets, MAH- Amdipharm Limited, Ireland. (PA 1142/002/002).

2.5.2. Overview of Biopharmaceutics

Carbimazole was first licensed in the UK on 20 June 1986, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of Carbimazole can be considered to be well established and to market the product under the generic name.

The current application Carbimazole 10 mg and 15 mg Tablets fulfills the bio-waiver criteria in accordance with the Bioequivalence guidance (CPMP/EWP/QWP//1401/98 Rev. 1/Corr**), thus the request for the waiver for in-vivo studies can be considered.

In-vitro multimedia dissolution testing of Carbimazole 20 mg Tablets [Flamingo Pharma (UK) Limited] have been performed and compared with the European reference product NeoMercazole 20 mg Tablets (MAH – Amdipharm Limited, Ireland). From the results it is evident that the products have similar *in-vitro* performance. Nevertheless, bioequivalence is established between these products.

In-vitro multimedia dissolution testing of Carbimazole 10 mg and 15 mg Tablets [Flamingo Pharma (UK) Limited] have been performed and compared with the bio-strength Carbimazole 20 mg (PL 43461/0035) [Flamingo Pharma (UK) Limited]. Results demonstrate that these products have similar dissolution profiles.

In addition to the in-vitro studies, Article 10(3) of the Directive 2001/83/EC (as amended) states that the applicant shall not be required to provide results of safety and/or efficacy.

Thus bioequivalence study is not required for lower strengths i.e. Carbimazole 10 mg and 15 mg Tablets, as general bio-waiver criteria is met accordance with the CHMP guidelines on the investigation of Bioequivalence (CPMP/EWP/QWP//1401/98 Rev. 1/Corr**) for waiver of in-vivo studies.

1. Carbimazole 10 mg and 15 mg Tablets have the same immediate release solid oral dosage form as that of the bio-strength 20 mg (i.e, uncoated tablets).
2. Carbimazole 10 mg and 15 mg Tablets are manufactured by the same manufacturer and by the same manufacturing process as that of the bio-strength 20 mg.
3. Qualitative composition of carbimazole 10 mg and 15 mg Tablets is same as that of the bio-strength 20 mg.
4. Composition of Carbimazole 10 mg and 15 mg Tablets are quantitatively proportional i.e the ratio between the amount of each excipient to the amount of active substance is same as that of the bio-strength 20 mg.
5. Carbimazole 10 mg, 15 mg and 20 mg Tablets exhibit comparable dissolution profile Similarity of dissolution profile is demonstrated between the bio-strength 20mg and additional strengths 10 mg & 15 mg in three different pH media (0.1N HCl, Acetate Buffer pH 4.5 and Phosphate Buffer pH 6.8).
6. Carbimazole is BCS class I drug and show linear pharmacokinetics over the therapeutic dosage range and Carbimazole does not fall under the narrow therapeutic drug category.[2 & 3]

Please refer to Module-5.3.1.3 for a more detailed discussion.

The pharmacodynamics, pharmacokinetics and toxicological properties of Carbimazole are well known. No new non-clinical and clinical studies were conducted for these applications, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

The presented literature supports the efficacy and safety of Carbimazole in the proposed indication and does not warrant any new or unexpected safety issues or concern.

2.5.3. Overview of Clinical Pharmacology

Carbimazole, a thionamide, is a pro-drug which undergoes rapid and virtually complete metabolism to the active metabolite, thiamazole, also known as methimazole. The method of action is believed to be inhibition of the organification of iodide and the coupling of iodothyronine residues which in turn suppress the synthesis of thyroid hormones.[1]

Pharmacokinetics:

Absorption: Carbimazole is rapidly metabolised to thiamazole. After oral ingestion, peak plasma concentrations of thiamazole, the active moiety, occur at 1 to 2 hours.

Distribution: The total volume of distribution of thiamazole is 0.5 L/kg. Thiamazole is concentrated in the thyroid gland. This intrathyroidal concentration of thiamazole has the effect of prolonging its activity. However, thiamazole has a shorter half-life in hyperthyroid patients than in normal controls and so more frequent initial doses are required while the hyperthyroidism is active.

Biotransformation: Thiamazole is moderately bound to plasma proteins. Carbimazole has a half-life of 5.3 to 5.4 hours. It is possible that the plasma half-life may also be prolonged by renal or hepatic disease. Thiamazole crosses the placenta and appears in breast milk. The plasma:milk ratio approaches unity.

Elimination: Over 90% of orally administered carbimazole is excreted in the urine as thiamazole or its metabolites. The remainder appears in faeces. There is 10% enterohepatic circulation.[1]

Benker G et. al. (1982), Absorption of methimazole and carbimazole is subject to considerable inter- individual variability, which is more pronounced for methimazole than for carbimazole. Propylthiouracil, but not methimazole, is bound to plasma proteins. After administration of carbimazole, only methimazole can be detected in serum and thyroid tissue. Conversion of carbimazole to methimazole appears to be an enzymatic process. Methimazole plasma levels are lower after carbimazole administration than after equal amounts (on a weight basis) of methimazole; 10 mg carbimazole are equivalent to 6-7 mg methimazole. Methimazole and propylthiouracil plasma levels decrease with time according to first-order kinetics. Serum half-life of propylthiouracil is about 1 hr, half-life of methimazole is 2-6 hr. Antithyroid drugs are concentrated by the thyroid gland. This accumulation is inhibited in iodine deficiency in animals. Inhibition of iodide organification is dependent on intrathyroidal rather than plasma concentration of antithyroid drugs. Intrathyroidal metabolism of antithyroid drugs involves

binding to thyroglobulin and stepwise oxidation. The main metabolite of propylthiouracil is PTU-SO_2H. A metabolite of methimazole, methylthiohydantoin, can be detected in plasma and urine. Propylthiouracil is rapidly coupled to glucuronic acid. A significant proportion of antithyroid drugs and their metabolites is excreted into bile and later reabsorbed (enterohepatic circulation). Fecal excretion is very low. In urine, small amounts of unchanged drugs are excreted together with glucuronides, methyl derivatives (only PTU) and unidentified metabolites. In pregnancy, methimazole half-life appears to be shortened. Methimazole and propylthiouracil can cross the placenta and are detected in the fetal circulation and thyroid. Concentrations in breast milk are very low, especially for propylthiouracil.[4]

Jansson, R et. al. (1985), the pharmacokinetics of methimazole following therapeutic doses were studied in healthy subjects, in thyrotoxic and hypothyroid patients before and after treatment to euthyroidism, and in patients with renal or hepatic insufficiency, using a highly sensitive gas chromatographic-mass spectrometric assay. Following intravenous administration of 10mg to healthy subjects, methimazole had an initial distribution half-life ($t_{1/2a}$ of 0.10 to 0.23 hours and an elimination half-life ($t_{1/2b}$) of 4.9 to 5.7 hours. The absolute bioavailability after oral administration of 10mg methimazole in the fasting state was high, with a mean of **93%.** The pharmacokinetic profiles showed small interindividual variations, although one of the hypothyroid patients had a rapid elimination half-life, in both the hypothyroid arid euthyroid state (2.6 and 2.4 hours, respectively). The elimination rate was not enhanced in the thyrotoxic patients but was slightly prolonged in the hypothyroid patients. There was no influence of renal insufficiency, but a prolonged elimination half-life was observed in patients with hepatic failure, the prolongation being proportional to the degree of impairment.[5]

Shenfield GM et. al. (1979), the bioavailability of two 5 mg tablets formulation of carbimazole [Neomercazole (A) and Carbazole (B)] has been compared in six euthyroid subjects. There was considerable inter-patient variation in absolute bioavailability although, for each subject, peak plasma concentrations of methimazole were similar with both formulations. The mean peak plasma concentrations were seen on average 62 min after administration of tablet A as compared to 40 min after tablet B. This is consistent with the finding that the disintegration and dissolution times were shorter for formulation B than for formulation A. The mean area under the plasma concentration curve and the 6 hr plasma concentration of methimazole tended to be greater after tablet A. These differences could be of significance in the treatment of thyrotoxicosis.[6]

Skellern GG et. al. (1980), the pharmacokinetics of methimazole after oral administration of carbimazole and methimazole, in hyperthyroid patients. Methimazole plasma concentrations were measured in two groups of hyperthyroid subjects after the oral administration of either carbimazole or methimazole. The HPLC method permitted the analysis of methimazole and its metabolite, 3-methyl-2- thiohydantoin, simultaneously. The methimazole plasma concentration v time curves for patients 1 to 10, who received 60 mg carbimazole orally, show that maximum plasma concentrations occurred between 30 min and 1 h, with an inflexion on the curve at around 4 h after drug administration with some patients. After oral administration of methimazole to patients 11 to 15, similar plasma concentration-time curves were obtained with less pronounced inflexions at 4 h. In patient 13 it was possible to measure the plasma concentration of the metabolite, 3-methyl-2- thiohydantoin, over a 24 h period. The biological half-life of 3-methyl-2-thiohydantoin in this patient, calculated from plasma concentrations at 12 and 24 h, was 13.5 h. In the majority of the other patients 3-methyl-2-thiohydantoin was only partially resolved from endogenous plasma material and was not accurately determinable. Incomplete absorption of carbimazole could explain particular high apparent volumes of distribution and apparent clearances.[7]

Skellern GG et. al. (1980), a high performance liquid chromatographic (HPLC) method was used to study the pharmacokinetics of methimazole after oral administration of carbimazole to women in various stages of pregnancy. In one patient it was possible to conduct the study in the first and third trimesters: there was an appreciable increase in the apparent clearance of methimazole. The mean half-life of methimazole was 2.02+0.22 h. based on the assumption of complete absorption and hydrolysis of carbimazole to methimazole the mean apparent clearance was found to be significantly higher in pregnant patients receiving 10 mg carbimazole than in non-pregnant patients receiving the same dose.[8]

The pharmacokinetic parameters of carbimazole are given in below table.

Table 1 The pharmacokinetic parameters of metimazole in pregnant hyperthyroid patients following oral administration of carbimazole

Subject number	*1*	*2*	*2a*	*3*	*4*	*5*	*6*	*7*	*Mean* ± s.e. mean
Body weight (kg)	55.3	69.2	80.5	50.9	59.2	62.1	47.2	57.7	60.3
Age (years)	26	35	35	26	25	29	23	23	28
Trimester	3	1	3	1	1	3	2–3	3	
Dose of carbimazole (mg)	10	10	10	10	10	10	20	20	
$\beta(h^{-1})$ ± s.e. mean	0.229 ± .056	0.617 ± .186	0.265 ± .081	0.266 ± .084	0.270 ± .029	0.405 ± .082	0.337 ± .064	0.592 ± .069	0.373 ± 0.054
$T_{\frac{1}{2}}$(h)	2.32	1.12	2.62	2.61	2.57	1.71	2.06	1.17	2.02 ± 0.22
Apparent $V_d\beta$(l)	26.9	14.5	48.5	38.1	26.5	30.1	12.2	19.8	27.1 ± 4.3
Apparent clearance (ml min^{-1})	134	149	214	169	119	203	68	196	157 ± 17
T_3 resin uptake ratio	0.97	0.89	0.68	1.25	1.1	1.04	1.38	0.70	
FTI[a] (nmol l^{-1})	146	140	73	457	145	321	402	92	

a Normal free thyroxine index range 55 to 144 nmol l^{-1}.

The carbimazole plasma concentration v time curves after oral administration of carbimazole are shown in below figure.

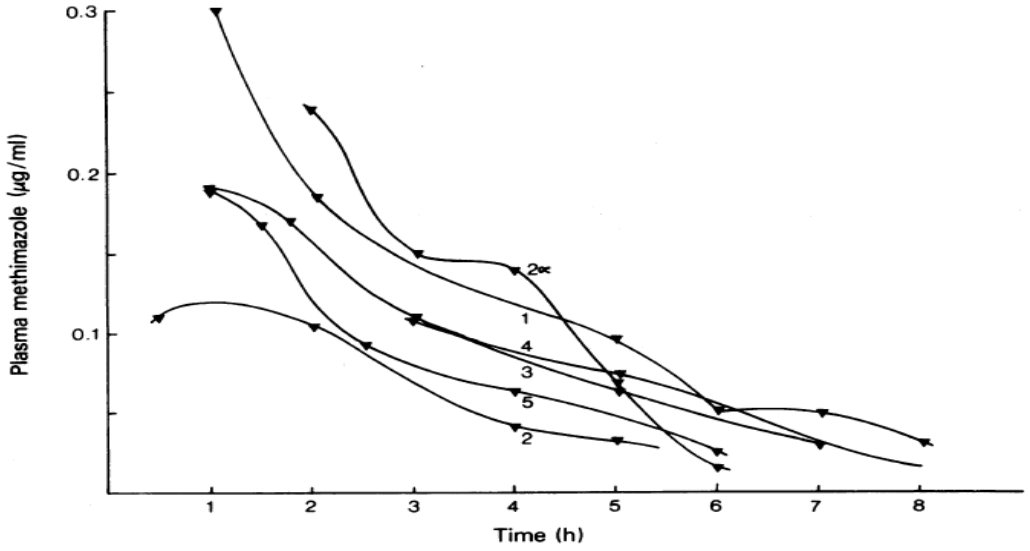

Figure 1 The methimazole plasma concentration *v* time curves from pregnant patients receiving carbimazole (10 mg).

Okuno A et. al. (1987), Methimazole concentrations in plasma and in the thyroid glands were measured by means of high-performance liquid chromatography. Pharmacokinetics of methimazole were studied after a single oral dose (175 μmol/m^2) in nine children and adolescent who were in the thyrotoxic state. Plasma levels of methimazole showed peak concentrations of 4.4 to 12.6 (median 9.2) μmol/l at 0.5 to 4 h after drug administration. Plasma half-life, area under the curve, and distribution volume ranged from 2.73 to 6.04 h, 32.8 to 77.9 μmol.l^{-1}.h^{-1}, and 0.516 to 0.913 l/kg, respectively. These pharmacokinetic parameters showed a wide variation among the patients, but were quite reproducible in the same subject. Intrathyroidal concentrations of methimazole were measured in another nine subjects including four adolescents and five adults who underwent thyroidectomy. The drug concentrations in the thyroid glands ranged between 3.5 and 23.8 μmol/kg tissue and were far higher than those in the plasma obtained at the time of surgery. In this series of experiments, the dose of the drug varied

from 76 to 319 µmol/m^2, time after the last dose to surgery from 5 to 24 h, and the mode of drug administration from a single to three divided doses. Among these variable factors, only the daily dose of methimazole corrected by body surface area showed significant correlation with the intrathyroidal concentration, whereas the time after the last dose of the drug and the mode of drug administration did not. Results revealed that methimazole was concentrated in the thyroid gland and that the intrathyroidal concentrations were maintained for 16 to 24 h in spite of a short plasma half-life. It is suggested that a single daily dose of methimazole is adequate for the treatment of Graves' disease in children and adolescents.[9]

Kampmann JP et. al. (1981), Organic antithyroid drugs used today include propylthiouracil and the mercaptoimidazolines, carbimazole and methimazole. They can be measured with accuracy and in small quantities in serum by gas-liquid chromatography, high performance liquid chromatography and radioimmunoassay. Bioavailability of these drugs varies from 80% to 95%. During absorption of carbimazole, which itself is inactive, is completely converted to methimazole. The total volume of distribution is about 40L for methimazole and around 30L for propylthiouracil, which is about 80% protein-bound, while methimazole is virtually non-protein-bound. Drug transfer across the placenta and into breast milk is also higher for the more lipid-soluble methimazole than for propylthiouracil, which is excreted into breast milk only in small quantities so that no harmful effect to the suckling infant is to be expected. Both the drugs are concentrated in the thyroid gland, exerting an effect on intrathyroidal iodine metabolism for periods exceeding those in which serum concentrations can be measured. Less than 10% of both drugs are excreted unchanged in the urine, but detailed metabolic pathways are unknown. The half-life of methimazole is 3 to 5 hours with a total clearance of about 200ml/minute. Propylthiouracil has a half-life of 1 to 2 hours with a clearance of around 120 ml/min/m^2. Some studies have shown an increased rate of metabolism of anti-thyroid drugs in hyperthyroidism, in particular for methimazole. No reliable information exists regarding pharmacokinetics of these agents in renal and hepatic failure or in children. The clearance of propylthiouracil is unchanged in the elderly. Several mechanisms for the inhibiting effect of these agents on intrathyroidal hormone metabolism have been suggested. In contrast to methimazole, propylthiouracil inhibits the peripheral conversion of thyroxine to triiodothyronine. Preliminary dose-response studies with propylthiouracil suggest a peak therapeutic serum concentration of above 4 micrograms/ml in the treatment of thyrotoxicosis. The choice between the antithyroid drugs is based more upon

personal preference and experience than on strict pharmacological principles, as no important differences exist between these drugs with regard to the rate of remission or frequency of occurrence of serious adverse reactions.[10]

Chuleegone Sornsuvit et. al. (2017), the pharmacokinetic parameters and bioequivalence of test and reference methimazole products were determined. A randomized, open-label, single-dose, two-treatment, two-period, two-sequence, crossover design between the administration of 5 mg methimazole tablets with a one-week wash-out period was conducted on 22 healthy Thai volunteers. Each volunteer was assigned parameters were determined, and 90% confidence intervals were calculated based on the log-transformed data. The mean C_{max}, $AUC_{0\text{-}48h}$, $AUC_{0\text{-}inf}$ and $T_{1/2}$ were 157.79 and 163.16 ng/ml, 1058.55 and 1040.52 ng.h/ml, 1160.16 and 1123.15 ng.h./ml and 6.29 and 6.01 h for the test and reference formulations, respectively. The mean ratios for the log-transformed data were -0.0261, 0.0234 and 0.0402 for C_{max}, and $AUC_{0\text{-}48h}$ and $AUC_{0\text{-}inf}$, respectively. In terms of the rate and to receive a single dose of the test or reference product. At 0.0, 10, 20, 30 and 45 min, and then 1, 1.33, 1.67, 2.0, 3.0, 4.0, 6.0, 8.0, 12.0, 24.0, 36.0 and 48.0 h after ingesting the pharmaceutical product, blood samples were collected. The plasma methimazole concentrations were analyzed by the validated LC-MS/MS. The Cmax, Tmax, T1/2, AUC0-48h, and AUC0-inf extent of the absorption, the test and reference methimazole 5 mg tablets were bioequivalent.[11]

Pharmacodynamics

Abbara A et. al. (2020), Graves' disease is the commonest cause of hyperthyroidism in populations with sufficient dietary iodine intake. Anti-thyroid drugs (ATD) are often used as the initial treatment for Graves' hyperthyroidism, however there is a paucity of data relating the dose of ATD therapy to the effect on thyroid hormone levels, increasing the risk of both over- and under-treatment. Author aimed to determine the pharmacodynamic response to the ATD carbimazole. Participants were patients (n = 441) diagnosed with Graves' disease at Imperial College Healthcare NHS Trust between 2009 and 2018. The main outcome measure was change in thyroid hormone levels in response to ATD. Baseline thyroid hormone levels were positively associated with TSH receptor antibody titres ($P < 0.0001$). Baseline free triiodothyronine (fT3) were linearly related to free thyroxine (fT4) levels in the hyperthyroid state (fT3 = fT4_0.97–11), and fell proportionately with carbimazole. The percentage falls in fT4 and fT3 per day were associated with carbimazole dose ($P < 0.0001$). The magnitude of fall in thyroid hormones after

the same dose of carbimazole was lower during follow up than at the initiation visit. The fall in thyroid hormone levels approximated to a linear response if assessed at least 3 weeks after commencement of carbimazole. Following withdrawal of antithyroid drug treatment, the risk of relapse was greater in patients with higher initial fT4, initial TSH receptor antibody titre, males, smokers, and British Caucasian ethnicity. Author identify a dose-response relationship for fall in thyroid hormones in response to carbimazole to aid in the selection of dose for Graves' hyperthyroidism.[12]

O'Malley BP et. al. (1988), In order to ascertain whether higher than conventional doses of carbimazole achieve more rapid control of thyrotoxicosis, 30 thyrotoxic patients were alternately allocated into two groups, group 1 (15 subjects) receiving a conventional starting dose of 45 mg orally daily and group 2 (15 subjects) a dose of 100 mg orally. In addition to weekly estimations of serum T4, T3, free T4, free T3 and TSH, the systolic time intervals ratio (STI), a measure of left ventricular contractility, was calculated as an accurate measure of peripheral thyroid hormone activity, the study end-point being a normal STI (0.26-0.32). None of the individuals studied experienced side-effects during the study period. Mean pre-treatment STI values for the two treatment groups were the same at entry (0.20). The mean recovery times for STI was 4.4 weeks (SE 0.3) in the high dose group and 5.9 weeks (SE 0.4) in the low dose group (P=0.0037). There was a definite trend towards a shorter recovery time for free T3 in the higher dose group (P=0.057) but no apparent differences for T4, T3 and free T4. Higher than conventional doses of carbimazole may be advisable in the initial treatment of severe thyrotoxicosis.[13]

Page SR et. al. (1996), a comparison of 20 or 40 mg per day of carbimazole in the initial treatment of hyperthyroidism. The optimal dosage regimen for carbimazole (CBZ) in the treatment of hyperthyroidism remains uncertain, despite clinical use of the drug for approximately fifty years. It compared the early clinical and biochemical responses to 20 or 40 mg/day of CBZ given as initial treatment for hyperthyroidism. Sixty-three (63) patient presenting with hyperthyroidism. Serum total and free thyroid hormones, serum TSH and SHBG were measured at baseline and at 4 and 10 weeks after start of therapy. Weight, pulse and a symptom questionnaire were also monitored at 6 and 12 weeks. The obtained results shows that the Patients randomized to a starting dose of 40 mg/day CBZ had lower total (98 ± 10 vs 158 ± 11 nmol/l, P< 0.001) and free T4 (19.4 ± 2.6 vs 35.2 ± 3.7 pmol/1, P < 0.001) and total (2.6 ± 0.3 vs 4.3 ± 0.4 nmol/1, P < 0.001) and free T3 (8.3 ± 1.0 vs 13.7 ± 1.2 pmol/1, P < 0.01) at 4 weeks

than those receiving 20 mg/day. Clinical responses at 6 and 12 weeks (weight, pulse, symptom score) and SHBG concentrations were similar. Drug-related hypothyroidism was less likely to occur at 4 and 10 weeks in those patient who initially received 20 mg CBZ/day, but this dose was less effective at controlling hyperthyroidism in those with more severe hyperthyroidism with baseline TT 4 > 260 nmol/l. In treating hyperthyroidism, 20 mg/day carbimazole is effective, convenient and has a lower risk than 40 mg/day of iatrogenic hypothyroidism in patients with mild or moderate hyperthyroidism. Higher doses are required for those with severe hyperthyroidism.[14]

McIver B et. al. (1996), Antithyroid drugs are effective in patients with hyperthyroidism due to Graves' disease, but the rate of recurrence after treatment is high. In a recent Japanese study, adjunctive treatment with thyroxine (T4) was associated with a recurrence rate 20 times lower than that among patients who received only an antithyroid drug. If these results are confirmed, combined therapy with an antithyroid drug and T4 might become the treatment of choice for all patients with Graves' hyperthyroidism. In this study, 111 patients (89 women and 22 men) who had Graves' hyperthyroidism were treated. All patients initially received 40 mg of carbimazole daily for one month. Then one group received carbimazole alone for 17 months (52 patients), and the other group received carbimazole plus T4 for 17 months and T4 alone for 18 months (59 patients). In the carbimazole group, the dose was adjusted after one month to maintain a normal serum thyrotropin concentration. In the carbimazole T4 group, the dose of carbimazole was not changed, but 100 mg of T4 per day was added to the regimen and the dose was adjusted to maintain an undetectable serum thyrotropin concentration (<0.04 μU per milliliter). At the time of analysis, 53 of the 111 patients had completed at least 3 months of follow-up (median, 12 months) after carbimazole was withdrawn. Hyperthyroidism recurred in eight patients in each group after a mean (±SD) of 6 ± 4 months in the carbimazole group and 7±4 months in the carbimazole-T4 group. There was no difference between the recurrence rates in the two groups, despite the fact that serum thyrotropin concentrations were undetectable in 73 percent of patients in the carbimazole-T4 group on at least 75 percent of their visits. It is concluded that the administration of T4 to patients with Graves' disease during carbimazole treatment and after its withdrawal neither delays nor prevents the recurrence of hyperthyroidism.[15]

Van der Bol JM et. al. (2011), to study the possible pharmacokinetic and pharmacodynamic interactions between irinotecan and methimazole. Plasma concentrations of the active irinotecan

metabolite SN-38 and its inactive metabolite SN-38- Glucuronide were both higher (a mean increase of 14 and 67%, respectively) with methimazole co-medication, compared to irinotecan monotherapy. As a result, the mean SN-38 glucuronidation rate increased with 47% during concurrent treatment. Other possible confounding factors did not change over time. Specific adverse events due to methimazole co-treatment were not seen. Additional in vitro experiments suggest that these results can be explained by induction of UGT1A1 by methimazole, leading to higher SN-38G concentrations. The prescribed combination of these drugs may lead to highly toxic intestinal SN-38 levels. Author therefore advise physicians to be very careful in combining methimazole with regular irinotecan doses, especially in patients who are prone to irinotecan toxicity.[16]

2.5.4. Overview of Efficacy

Azizi, F et. al. (2021), Methimazole (MMI) is the treatment of choice for patients with Graves' disease. The major drawback of this treatment is the relapse of hyperthyroidism in half of the patients after discontinuation of the recommended conventional 12–18 months of MMI treatment. TSH receptor antibody (TRAb) concentration is recognized as the strongest predictor of hyperthyroidism relapse. In this case report, efficacy of low-dose MMI to control hyperthyroidism even after multiple recurrences in the setting of normal TRAb concentrations is shown. An 80-year-old Iranian woman with Graves' disease was treated with MMI for 31 years. While receiving treatment, she always had a normal serum TRAb concentration; however, three times during the 31 years she decided to stop MMI therapy, and each time the disease recurred 16–21 months after MMI withdrawal. It is noteworthy that she maintained euthyroidism with the low-dose 1.25–2.5 mg MMI daily without any adverse events during three decades of treatment. Normal serum TRAb is not a sufciently strong marker to predict relapse of Graves' hyperthyroidism. Long-term therapy with low-dose MMI is an efective and safe treatment to sustain euthyroidism.[17]

Wu X et. al. (2022), this study aimed to systematically evaluate the effectiveness and safety of methimazole combined with levothyroxine for treating hyperthyroidism in children. Meta-analysis results indicated that compared with methimazole alone (control group), the experimental group administered methimazole + levothyroxine had no evident difference in the level of thyroid-stimulating hormone [standardized mean difference (SMD) =–0.34, 95% confidence interval (CI): –1.02, 0.35, P=0.33], but notably improved the efficacy of clinical treatment of hyperthyroidism in children [odds ratio (OR) =5.77, 95% CI: 2.62, 12.74, P<0.001]. Meanwhile, the experimental group had lower adverse reaction rates (OR =0.28, 95%CI: 0.19, 0.40, P<0.001), free triiodothyronine (FT3) level (SMD =–0.85, 95% CI: –1.57, 0.13, P=0.02), free tetraiodothyronine (FT4) level (SMD =–0.94, 95% CI: –1.59, –0.30, P=0.004) and reduced thyroid volume (SMD =–1.3, 95% CI: –1.67, 0.93, P<0.001). Using methimazole + levothyroxine to treat hyperthyroidism in children can raise the levels of FT3 and FT4, reduce the thyroid volume, improve clinical efficacy, and lower the adverse reaction rate of patients.[18]

Mafauzy M et. al. (1993), Carbimazole in 3 divided daily doses is commonly prescribed for the treatment of thyrotoxicosis. However, based on its long intra-thyroid half-life, the drug may be effective when used as a single or twice daily dose. This study was undertaken to determine the

effect of once, twice or thrice daily doses of carbimazole on thyroid function in patients with thyrotoxicosis. Seventy previously untreated thyrotoxic patients were randomly allocated to receive carbimazole 30 mg once (group-1), 15 mg twice (group-2) and 10 mg thrice (group-3) daily. All patients were also prescribed propranalol 20 mg thrice daily for the first 4 weeks. Blood was taken for total T3, T 4, TSH, blood counts and liver enzymes determinations at the beginning and at 6 weeks of treatment. Only 48 (68.6%) patients were included in the analysis, as the rest defaulted follow-up (20.0%) or blood samples were not available at review (11.4%) Of the 48 patients, 17 were in group-1, 16 in group-2 and 15 in group-3. Following 6 weeks of treatment, there was no significant difference in the mean serum levels of total T3 and T4 between the 3 groups. However, there was a significant decrease in the mean serum levels of total T3 and T4 as compared to the start of the treatment. Four patients (23.5%) in group-1, 4 patients (25%) in group-2 and 3 patients (20%) in group-3 were still thyrotoxic at 6 weeks of treatment, whilst 10 patients (58.8%) in group-1, 6 patients (37.5%) in group-2 and 3 (20%) in group-3 were biochemically hypothyroid. There was no significant difference in total white cell count, serum alanine aminotransferase (ALT) and aspastate transaminase (AST) values between the 3 groups. In conclusion, carbimazole given in once or twice daily doses was as effective as when given in thrice daily doses in the treatment of thyrotoxicosis with no adverse effect on white cell count and liver enzymes.[19]

EI Refaei SM et. al. (2008), the aim of this study is to assess the effect of long-term anti-thyroid drug intake on the success rate of iodine-131 (131-I) treatment of Graves' hyperthyroidism, and to explore other clinical/laboratory factors that may predict/affect the treatment outcome. Fifty-eight patients with Graves' disease were referred for radioactive iodine therapy after failure of medical treatment, which was given for at least 6 months. Antithyroid drug (carbimazole) was stopped for at least 2 days before administration of a fixed dose of 370 MBq. Treatment outcome was determined at the end of 1-year follow-up after iodine administration. Treatment success was reported if the thyroid hormonal profile indicated euthyroid or hypothyroid state. One year after ^{131}I administration, 19% of patients were still hyperthyroid (treatment failure), 15.5% became euthyroid and 65.5% were hypothyroid (treatment success, 81%). No statistically significant correlation was found between treatment outcome and patient's age at the time of I administration (P=0.20); duration of medical treatment before ^{131}I administration (P=0.22) and duration of stoppage of medical treatment before ^{131}I intake (P=0.15). In contrast, there was

significant association between treatment outcome and pretreatment Tc99m-thyroid uptake (P=0.0001), thyroid size (P=0.001) and TSH level (P=0.04). Using receiver operator characteristic curve analysis, we generated a cut-off value for thyroid uptake (18%) and thyroid weight (70 g) to predict response to 370 MBq of ^{131}I. The 18% thyroid uptake cut-off value predicted treatment outcome with 93.6% sensitivity, 100% specificity and 94.8% accuracy, whereas the 70 g thyroid weight predicted treatment outcome with sensitivity, specificity and accuracy of 80.9, 72.7 and 79.3%, respectively. Long-term carbimazole treatment will not increase the failure rate of ^{131}I treatment in patients with Graves' disease if the drug was discontinued for at least 02 days before iodine administration. A fixed dose of 370 MBq is efficient in patients with Tc99m-pertechnetate thyroid uptake less than 18% and gland weight less than 70 g. Patients with larger goitres and/or higher thyroid uptake level will probably need a higher dose of radioactive iodine.[20]

MacFarlane IA et. al. (1983), Twenty-one patients with hyperthyroid Graves' disease were treated with carbimazole 30 mg daily, given as a single dose. Propranolol was also given for the first 3 weeks. All became clinically euthyroid with normal serum thyroxine (T4) levels, usually within 1-3 months. Patients with large goitres and raised serum alkaline phosphatase concentrations took longer to respond. In 19 patients a positive thyroid stimulating hormone (TSH) response to intravenous thyrotrophin releasing hormone (TRH) developed. Carbimazole was stopped soon after (median time of treatment 18 weeks, range 9-41 weeks) and 18 patients have been followed. Seven of these (39%) have remained in remission from hyperthyroidism for more than one year (median 77 weeks). Carbimazole 30 mg once daily is a convenient and effective treatment for hyperthyroid Graves' disease. Many patients will achieve prolonged remissions if treatment is stopped when serum T3 and T4 levels are in the low-normal range, usually 2-4 months after clinical euthyroidism has been reached.[21]

2.5.5. Overview of Safety

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, leucopenia 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 and malaise and should be instructed to stop the drug and to seek medical advice immediately. In such patients, white blood cell counts should be performed immediately, particularly where there is any clinical evidence of infection.

Generalised lymphadenopathy.

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

Endocrine disorders
Insulin autoimmune syndrome (with pronounced decline in blood glucose level).

Nervous system disorders
Headache, neuritis, polyneuropathy.

Vascular disorders
Bleeding.

Gastrointestinal disorders
Nausea, mild gastrointestinal disturbance.
Loss of sense of taste has been observed.
Acute salivary gland swelling,
Acute pancreatitis.

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

Skin and subcutaneous tissue disorders
Skin rashes, pruritus, urticaria. Hair loss has been occasionally reported.

Severe cutaneous hypersensitivity reactions have been reported in both adult and paediatric patients, including Stevens-Johnson syndrome (very rare including isolated reports: severe forms, including generalised dermatitis, have only been described in isolated cases).

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

General disorders and administration site conditions
Fever, malaise.

Injury, poisoning and procedural complications
Bruising

Paediatric population
Frequency, type and severity of adverse reactions in children appear to be comparable with those in adults. [1]

Special warnings and precautions for use:

Bone marrow depression including neutropenia, eosinophilia, leucopenia 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 and malaise and should be instructed to stop the drug and to seek medical advice immediately. In such patients, white 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 radioiodine (to avoid thyroid crisis).

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.

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.

There is a risk of cross-allergy between carbimazole, the active metabolite thiamazole (methimazole) and propylthiouracil.

There have been post-marketing reports of acute pancreatitis in patients receiving carbimazole or its active metabolite thiamazole. 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.

<u>Women of childbearing potential and pregnancy</u>
Women of childbearing potential have to use effective contraceptive measures during treatment.

The use of carbimazole in pregnant women must be based on the individual benefit/risk assessment. If carbimazole is used during pregnancy, the lowest effective dose without additional administration of thyroid hormones should be administered.
Close maternal, foetal and neonatal monitoring is warranted.

<u>Carbimazole contains lactose</u>
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Carbimazole contains sucrose
Patients with the rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-iso maltase insufficiency should not take this medicine.[1]

Fertility, pregnancy and lactation:

Women of childbearing potential
Women of childbearing potential have to use effective contraceptive measures during treatment.

Pregnancy
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 who have been treated with carbimazole.

However, 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 (congenital scalp defects), 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.

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.

Hyperthyroidism in pregnant women should be adequately treated to prevent serious maternal and foetal complications.

Carbimazole is able to cross the human placenta.

Based on human experience from epidemiological studies and spontaneous reporting, carbimazole is suspected to cause congenital malformations when administered during pregnancy, particularly in the first trimester of pregnancy and at high doses.

Reported malformations include aplasia cutis congenita, craniofacial malformations (choanal atresia; facial dysmorphism), exomphalos, oesophageal atresia, omphalomesenteric duct anomaly, and ventricular septal defect.

Carbimazole must only be administered during pregnancy after a strict individual benefit/risk assessment and only at the lowest effective dose without additional administration of thyroid hormones. If carbimazole is used during pregnancy, close maternal, foetal and neonatal monitoring is recommended.

Breast-feeding
Carbimazole is secreted in breast milk and, if treatment is continued during lactation, the patient should not continue to breast-feed her baby.[1]

Contraindications:

Hypersensitivity to the active substance or to any of the excipients

- Serious, pre-existing haematological conditions,
- Severe hepatic insufficiency
- Patients with a history of acute pancreatitis after administration of carbimazole or its active metabolite thiamazole. [1]

Overdose:

Symptoms
No symptoms are likely from a single large dose.

Management
No specific treatment is indicated.[1]

Interaction with other medicinal products and other forms of interaction:

Little is known about interactions.

Interaction studies have not been performed in paediatric patients.

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. Additional monitoring of PT/INR should be considered, especially before surgical procedures.

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

Co-administration of prednisolone and carbimazole may result in increased clearance of prednisolone.

Carbimazole may inhibit the metabolism of erythromycin, leading to reduced clearance of erythromycin.

Serum digitalis levels may be increased when hyperthyroid patients on a stable digitalis glycoside regimen become euthyroid; a reduced dosage of digitalis glycosides may be needed.

Hyperthyroidism may cause an increased clearance of beta-adrenergic blockers with a high extraction ratio. A dose reduction of beta blockers may be needed when a hyperthyroid patient becomes euthyroid.[1]

Literature data

Rivkees SA et. al. (2010), Graves' disease is the most common cause of hyperthyroidism in the pediatric population. Antithyroid medications used in children and adults include propylthiouracil (PTU) and methimazole (MMI). At center author have routinely used MMI for Graves' disease therapy. Author goals are to provide insights into adverse events that can be associated with MMI use. A reviewed the adverse events associated with MMI use in last one hundred consecutive pediatric patients treated with this medication. The range in the patient age was 3.5 to 18 years. The patients were treated with an average daily dose of MMI of 0.3 ± 0.2 mg/kg/day. Adverse events attributed to the use of the medication were seen in 19 patients at 17 ± 7 weeks of therapy. The most common side effects included pruritus and hives, which were seen in 8 patients. Three patients developed diffuse arthralgia and joint pain. Two patients developed neutropenia. Three patients developed Stevens-Johnson syndrome, requiring hospitalization in 1 child. Cholestatic jaundice was observed in 1 patient. No specific risk-factors for the development of adverse events were identified. MMI use in children is associated with a low but real risk of minor and major side effects.[22]

Andersen SL et. al. (2019), the study looked at the frequency in over one million children born between 1997 and 2016. The researchers compared how often the birth defects occurred in children who were exposed to MMI, or PTU or not exposed at all to these antithyroid drugs. The researchers found that birth defects were seen in only 6.7% of children who were not exposed to

ATDs, but were higher for those children exposed to MMI, at 9.6%, and 8.3% for those exposed to PTU. The researchers also checked specifically only the kinds of birth defects previous studies have found were especially common in children of mothers who take antithyroid drugs. Of the children who were not exposed to antithyroid drugs only 3.1% had these kinds of birth defects, but of the children who were exposed to MMI, 6.4% had these kinds of birth defects and only 4.4% were seen in PTU exposed children. In the children who were exposed to PTU, the birth defects were found only in the face, neck and urinary system, while children who were exposed to MMI, the birth defects involved many organs: some had aplasia cutis (lack of skin in the scalp), esophageal or choanal atresia (back of the nasal passage is blocked) and omphalocele (abdominal wall defect with abdominal organs misplaced outside the abdomen). In children of women who switched from MMI to PTU during the first trimester, 5% had this specific type of birth defects as compared to 3.1% in the unexposed children. When the authors looked at whether a mother's hyperthyroidism in general seemed to cause birth defects, they found no evidence that it did. However, they did find that that in the women who specifically had overt hypothyroidism (low thyroid hormone levels), there were more birth defects. If carbimazole is used during pregnancy, close maternal, foetal and neonatal monitoring is recommended.[23]

Azizi F et. al. (2011), poorly treated or untreated maternal overt hyperthyroidism may affect pregnancy outcome. Fetal and neonatal hypo- or hyper-thyroidism and neonatal central hypothyroidism may complicate health issues during intrauterine and neonatal periods. To review articles related to appropriate management of hyperthyroidism during pregnancy and lactation. A literature review was performed using MEDLINE with the terms 'hyperthyroidism and pregnancy', 'antithyroid drugs and pregnancy', 'radioiodine and pregnancy', 'hyperthyroidism and lactation', and 'antithyroid drugs and lactation', both separately and in conjunction with the terms 'fetus' and 'maternal.' Antithyroid drugs are the main therapy for maternal hyperthyroidism. Both methimazole (MMI) and propylthiouracil (PTU) may be used during pregnancy; however, PTU is preferred in the first trimester and should be replaced by MMI after this trimester. Choanal and esophageal atresia of fetus in MMI-treated and maternal hepatotoxicity in PTU-treated pregnancies are of utmost concern. Maintaining free thyroxine concentration in the upper one-third of each trimester-specific reference interval denotes success of therapy. MMI is the mainstay of the treatment of post partum hyperthyroidism, in particular during lactation. It is conclude that management of hyperthyroidism during pregnancy and

lactation requires special considerations and should be carefully implemented to avoid any adverse effects on the mother, fetus, and neonate.[24]

Laurberg P et. al. (2014), to study antithyroid drug use in early pregnancy and birth defects: time windows of relative safety and high risk in therapy of endocrine disease. Antithyroid drugs (ATDs) may have teratogenic effects when used in early pregnancy. To review the association between the time period of ATD exposure in early pregnancy and the development of birth defects. It is identified publications on birth defects after early pregnancy exposure to the ATDs methimazole [MMI; and its prodrug carbimazole (CMZ)] and propylthiouracil (PTU). Cases of birth defects after ATD treatment had been initiated or terminated within the first 10 weeks of pregnancy were identified and studied in detail. A total of 92 publications were read in detail. Two recent large controlled studies showed ATD-associated birth defects in 2-3% of exposed children, and MMI/CMZ-associated defects were often severe. Out of the total number of publications, 17 included cases of birth defects with early pregnancy stop/start of ATD treatment, and these cases suggested that the high risk was confined to gestational weeks 6-10, which is the major period of organogenesis. Thus, the cases reported suggest that the risk of birth defects could be minimized if pregnant women terminate ATD intake before gestational week 6. Both MMI and PTU use in early pregnancy may lead to birth defects in 2-3% of the exposed children. MMI-associated defects are often severe.[25]

Wu X et. al. (2013), Efficacy and safety of methimazole ointment for patients with hyperthyroidism. Oral methimazole has been widely used to treat hyperthyroidism, but its usage is restricted by its adverse systemic effects. The aim of this study was to investigate the efficacy and safety of methimazole ointment for the treatment of hyperthyroidism. One hundred forty-four (144) subjects with hyperthyroidism were initially enrolled. These patients were initially divided into two groups and given the following treatments for 12 weeks: patients in group-A received 5% methimazole ointment applied to the skin around the thyroid and an oral placebo and patients in group-B received methimazole tablets and placebo ointment. One hundred thirty-one (131) subjects were included in the final analysis. Therapeutic efficacy was assessed via the levels of free triiodothyronine (T_3) and thyroxine (T_4) in the serum and by bi-weekly monitoring of the symptoms of thyrotoxicosis. Adverse effects were recorded. Fifty-nine (89.40%) patients in group-A and 57 (87.69%) patients in group-B were euthyroid and experienced alleviation of thyrotoxicosis symptoms (complete control; $P>0.05$). The median times required to achieve

complete control for the patients in the two groups were 6.5 weeks and 6.4 weeks for group-A and Group-B, respectively (P>0.05). Systemic adverse effects (e.g., rash, liver dysfunction, leucopenia, etc.) were significantly less common in group-A (1.5%) than in group-B (12.3%; P<0.05). This study showed that methimazole ointment has a clinical efficacy similar to that of oral tablets, but methimazole ointment caused fewer systemic adverse effects in patients with hyperthyroidism.[26]

Karmisholt J et. al. (2022), In this prospective multicenter study with patients newly diagnosed with Graves' hyperthyroidism (GH), author studied the timing and characteristics of adverse drug reactions in patients treated with anti-thyroid drugs (ATD) for up to 48 months. Patients with GH were treated with ATD until remission and hereafter with a low-dose regime to keep the patients in remission. The patients were followed with blood samples and recording of adverse events approximately every second month for the first 2 years and every third month for the following 2 years. Author included 208 patients and the patients were treated for a median of 22 (range: 0.5–49) months. Ten percent of the patients experienced adverse drug reactions and 75% of the cases occurred during the first 6 months. After 24 months, the methimazole dose was lowered to 5 mg/day, and after this time point, no further adverse drug reactions were recorded. Skin reactions were the most prominent reaction, comprising 68% of the registered reactions, and no hepatic and bonemarrow affection was recorded. Author report the frequency, timing of occurrence, and characteristics of adverse drug reactions when treating GH with the ATD drug methimazole for up to 48 months. Long-term low-dose methimazole treatment can be a cost-effective and straightforward treatment option if adverse drug reactions such as severe hepatic and bone marrow affection are kept in mind.[27]

Kasraee B et. al. (2008), Methimazole is an oral antithyroid compound that exhibits a skin-depigmenting effect when used topically. However, the effect of topical methimazole on thyroid function has not been reported. This study was aimed at assessing the safety of topical methimazole used to treat pigmented lesions, without affecting thyroid hormones due to systemic delivery. The pharmacokinetics of methimazole, either applied in the form of a 5% topical formulation to facial skin or taken orally in the form of a 5-mg tablet by 6 volunteers, were determined. In addition, the effect of long-term topical applications of 5% methimazole on the function of the thyroid gland in 20 patients with epidermal melasma was determined following 6 weeks of once-daily application. Cutaneous adverse effects of topical methimazole were

determined. From 15 min up to 24 h after application, methimazole was undetectable in the serum of the individuals receiving single topical methimazole dosing. Methimazole, however, was detected in serum after 15 min of oral administration and remained detectable in serum up to 24 h after administration. Long-term topical methimazole applications in melasma patients did not induce any significant changes in serum TSH, free thyroxine and free triiodothyronine levels. Topical methimazole was well tolerated by the patients and did not induce any significant cutaneous side effects. Present data together with the previously shown non-cytotoxic and non-mutagenic characteristics of methimazole indicate that this agent could be considered as a safe skin-depigmenting compound for topical treatment of skin hyperpigmentary disorders in humans.[28]

No epidemiological data on use of methimazole and cancer were found. However, two analyses were published of one cohort study conducted in the United Kingdom and the USA of the cancer risk of patients, mainly women, with hyperthyroidism who had been treated with anti-thyroid drugs. The earlier analysis showed more malignant thyroid neoplasms in patients receiving these drugs than in those treated with surgery or ^{131}I, but the excess may have been due to closer surveillance of the patients given drugs owing to more frequent use of thyroidectomy. In the later analysis, patients with hyperthyroidism treated only with anti-thyroid drugs had a modest increase in the risk for death from cancer, due chiefly to oral cancer and cancer of the brain. Neither report provided information on the type, quantity or dates of anti-thyroid drug use. Two case–control studies of cancer of the thyroid showed no significant association with treatment with anti-thyroid medications. Two case–control studies of cancer of the thyroid showed no significant association with treatment with anti-thyroid medications.[29]

Azizi F et. al. (2005), to investigate the long-term effects of continuous methimazole (MMI) therapy. Five hundred and four patients over 40 years of age with diffuse toxic goiter were treated with MMI for 18 months. Within one year after discontinuation of MMI, hyperthyroidism recurred in 104 patients. They were randomized into 2 groups for continuous antithyroid and radioiodine treatment. Numbers of occurrences of thyroid dysfunction and total costs of management were assessed during 10 years of follow-up. At the end of the study, 26 patients were still on continuous MMI (group 1), and of 41 radioiodine-treated patients (group 2), 16 were euthyroid and 25 became hypothyroid. Serum thyroid and lipid profiles, bone mineral density, and echocardiography data were obtained. There was no significant difference in age,

sex, duration of symptoms and thyroid function between the two groups. No serious complications occurred in any of the patients. The cost of treatment was lower in group 1 than in group 2. At the end of 10 years, goiter rate was greater and antithyroperoxidase antibody concentration was higher in group 1 than in group 2. Serum cholesterol and low density lipoprotein-cholesterol concentrations were increased in group 2 as compared with group 1; relative risks were 1.8 (1.12–2.95, P , 0.02) and 1.6 (1.09–2.34, P , 0.02) respectively. Bone mineral density and echocardiographic measurements were not different between the two groups. Long-term continuous treatment of hyperthyroidism with MMI is safe. The complications and the expense of the treatment do not exceed those of radioactive iodine therapy.[30]

2.5.6. Benefits and Risks Conclusions

Carbimazole is an anti-thyroid agent and sulfur-containing imidazole derivatives. Carbimazole, a thionamide, is a pro-drug which undergoes rapid and virtually complete metabolism to the active metabolite, thiamazole, also known as methimazole.

The method of action is believed to be inhibition of the organification of iodide and the coupling of iodothyronine residues which in turn suppress the synthesis of thyroid hormones.

The clinical importance of carbimazole is in adults and children in all conditions where reduction of thyroid function is required. Such conditions are:

1. Hyperthyroidism.
2. Preparation for thyroidectomy in hyperthyroidism.
3. Therapy prior to and post radio-iodine treatment.

Bioequivalence study has been performed on the Carbimazole 20 mg Tablets in which the pharmacokinetic profile of generic product Carbimazole 20 mg Tablets is compared with the pharmacokinetic profile of the reference product NeoMercazole 20 mg Tablets of Amdipharm Ireland, in compliance with the Good Clinical Practice and EMA Guideline on the Investigation of Bioequivalence; CPMP/EWP/QWP/1401/98 Rev.1/Corr**.

Additional bioequivalence study is not required for the subjected lower strengths i.e. Carbimazole 10 mg and 15 mg Tablets, as they meet the requirements of biowaiver criteria stipulated in the CHMP guidelines on the investigation of Bioequivalence (CPMP/EWP/QWP//1401/98 Rev. 1/Corr**) for waiver of in vivo studies.

Extensive data obtained from randomized clinical trials, post marketing analyses and reports to regulatory agencies demonstrate that the safety and tolerability of carbimazole or methimazole in a large number of patients.

No additional pharmacological, toxicological or clinical work has been conducted or submitted as part of this generic application. The published literature supports the efficacy and safety of Carbimazole in the proposed indication. The available literature shows that there are no new or unexpected safety issues or concerns. Thus, carbimazole is safe and well tolerated agent for proposed indication.

In conclusion, using carbimazole according to the instruction does not constitute any excessive risk to a patient or the community provided that contraindication, precaution and possible interactions are adequately taken into account.

2.5.7. Literature References

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