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## 2.4 Non-clinical Overview

### 2.4.1 Overview of the Nonclinical Testing Strategy

The non-clinical testing strategy for this application consists of a synopsis and critical overview of the preclinical publicly available data for carbimazole.

Carbimazole is an anti-thyroid agent. It is indicated in adults and children in all conditions where reduction of thyroid function is required.<sup>1</sup>

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.

The current application of medicinal product Carbimazole 10 mg and 15 mg Tablets is a hybrid application which comes under Regulation 52B of the Human Medicines Regulations 2012, as amended [previously Article 10(3) of Directive 2001/83/EC, as amended]. This application for generic product Carbimazole 10 mg and 15 mg Tablets, submitted under Regulation 52B (EC Article 10(3)), cross-referring to a reference product NeoMercazole® 20 mg Tablets, Amdipharm UK Limited. The reference product has been authorized in the EU and UK for more than 10 years thus; no additional non-clinical studies have been performed. The efficacy and safety profile of carbimazole is a well-known.

The non-clinical overview summarized the relevant scientific literature on pharmacodynamic, pharmacokinetics and toxicological properties of carbimazole.

### 2.4.2 Pharmacology

Daminct S et. al. (2014), Pharmacological management of feline hyperthyroidism offers a practical treatment option for many hyperthyroid cats. Two drugs have been licensed for cats in the last decade: methimazole and its pro-drug carbimazole. On the basis of current evidence and available tablet sizes, starting doses of 2.5 mg methimazole twice a day and 10 to 15 mg once a day for the sustained release formulation of carbimazole are recommended. These doses should

then be titrated to effect in order to obtain circulating total thyroxine (TT4) concentrations in the lower half of the reference interval. Treated cases should be monitored for side-effects, especially during the first months of treatment. Some side-effects may require discontinuation of treatment. At each monitoring visit, clinical condition and quality of life should also be evaluated, with special attention to possible development of azotaemia, hypertension and iatrogenic hypothyroidism. When euthyroidism has been achieved, monitoring visits are recommended after 1 month, 3 months and biannually thereafter. Cats with pre-existing azotaemia have shorter survival times. However, development of mild azotaemia during the initial course of treatment, unless associated with hypothyroidism, does not appear to decrease survival time.<sup>2</sup>

Genter MB et. al. (1998), Carbimazole (2-carbethoxythio-1-methylimidazole) is a thiocarbamide drug used in the treatment of hyperthyroidism in humans. Side effects associated with carbimazole treatment are reported to include impaired taste, impaired olfaction, and hearing loss. The structurally similar antihyperthyroid drug methimazole (1-methyl-2-mercaptoimidazole), also reportedly associated with impaired taste and olfaction in humans, has recently been demonstrated by this laboratory to be an olfactory toxicant by both the oral and intraperitoneal routes of exposure in rodents. A systematic evaluation of sensory system effects of these compounds, either in rodents or humans, is not available in the literature. Male Long-Evans rats were used to evaluate the auditory and olfactory toxicity of carbimazole by two routes of exposure. Histopathological evaluation of nasal cavities from rats administered carbimazole via i.p. and oral routes revealed olfactory mucosal damage and early evidence of repair; a No-Observed Effect Level (NOEL) of 100 mg/kg was observed for orally administered carbimazole. Further, these studies demonstrate evidence for the generation of the olfactory toxic metabolites of carbimazole by the olfactory mucosa itself, as incubation of carbimazole with an olfactory S9 preparation resulted in NADPH dependent degradation of carbimazole. Evaluation of the auditory startle response in carbimazole-treated rats revealed no deficits, demonstrating that carbimazole does not cause a global loss of hearing in rats.<sup>3</sup>

Peterson ME et. al. (1988), the efficacy and safety of the antithyroid drug methimazole were evaluated over a 3-year period in 262 cats with hyperthyroidism. In 181 of the cats, methimazole was administered for 7 to 130 days (mean, 27.7 days) as a preoperative preparation for thyroidectomy. The remaining 81 cats were given methimazole for 30 to 1,000 days (mean, 228 days) as sole treatment for the hyperthyroid state. After 2 to 3 weeks of methimazole therapy (10

to 15 mg/d), the mean serum thyroxine (T4) concentration decreased significantly (P less than 0.001) from a pretreatment value of 12.1 micrograms/dl to 2.1 micrograms/dl. The final maintenance dose needed to maintain euthyroidism in the 81 cats that were given methimazole as sole treatment for hyperthyroidism ranged from 2.5 to 20 mg/d (mean, 11.9 mg/d). Clinical side effects developed in 48 (18.3%) cats (usually within the first month of therapy), which included anorexia, vomiting, lethargy, self-induced excoriation of the face and neck, bleeding diathesis, and icterus caused by hepatopathy. Mild hematologic abnormalities developed in 43 (16.4%) cats (usually within the first 2 months of treatment), which included eosinophilia, lymphocytosis, and slight leukopenia. In ten (3.8%) cats, more serious hematologic reactions developed including agranulocytosis and thrombocytopenia (associated with bleeding). These hematologic abnormalities resolved within 1 week after cessation of methimazole treatment.<sup>4</sup>

Trepanier LA et. al. (2006), Radioiodine is considered the treatment of choice for hyperthyroidism, but in some situations, methimazole therapy is preferred, such as in cats with pre-existing renal insufficiency. Methimazole blocks thyroid hormone synthesis, and controls hyperthyroidism in more than 90% of cats that tolerate the drug. Unfavorable outcomes are usually due to side effects such as gastrointestinal (GI) upset, facial excoriation, thrombocytopenia, neutropenia, or liver enzyme elevations; warfarin-like coagulopathy or myasthenia gravis have been reported but are rare. Because restoration of euthyroidism can lead to a drop in glomerular filtration rate, all cats treated with methimazole should be monitored with BUN and creatinine, in addition to serum T4, complete blood count, and liver enzymes. Transdermal methimazole is associated with fewer GI side effects, and can be used in cats with simple vomiting or inappetence from oral methimazole. Hypertension may not resolve immediately when serum T4 is normalized, and moderate to severe hypertension should be treated concurrently with atenolol, amlodipine, or an ACE inhibitor. Alternatives to methimazole include carbimazole, propylthiouracil, or iodinated contrast agents.<sup>5</sup>

Upadhyaya L et. al. (1993), Effect of L-thyroxine and carbimazole on brain biogenic amines and amino acids content and circulating levels of thyroid hormones has been investigated in rats. L-thyroxine treatment caused marked elevation of 5-HT, histamine and glutamate along with the decline in the level of GABA whereas administration of carbimazole had a contrary effect on rat hypothalamus. Further, L-thyroxine administration also raised histamine as well as glutamate content and decreased GABA level in thalamic region of the rat brain but carbimazole treatment reduced 5-HT and glutamate content in this area of the rat brain. Similarly, cortical content of 5-

HT and histamine also increased following L-thyroxine administration whereas carbimazole treatment lowered 5-HT, histamine and glutamate levels. Simultaneously, there was a considerable rise in the circulating levels of T3 and T4 in L-thyroxine-treated rats and a marked reduction in their levels in carbimazole-treated rats. There is a positive correlation between these amines and the thyroid hormone level. Thus, the results suggest that L-thyroxine and carbimazole administration cause marked alteration in biogenic amines and amino acids in rat brain, which may have an important role in the functioning of thyroid gland.<sup>6</sup>

Hill KE et. al. (2015), there are no significant differences between the pharmacokinetics of methimazole and carbimazole in cats. The *in vivo* action of carbimazole is due to its rapid metabolism to methimazole. After the oral administration of 5 mg of carbimazole to nine cats, serum concentrations of methimazole increased and serum concentrations of carbimazole were undetectable in eight cats. The mean absolute bioavailability of methimazole in healthy (76 to 81%) and hyperthyroid (81%) cats is similar to the reported absolute bioavailability of controlled release carbimazole in healthy cats (88%).<sup>7</sup>

Hill KE et. al. (2011), previous studies on transdermal methimazole have used pluronic lecithin organogel as the vehicle. This might not be the most suitable vehicle for a lipophilic drug, such as methimazole. Once daily transdermal administration of a novel lipophilic formulation of methimazole is as safe and effective as oral carbimazole in treating hyperthyroidism in cats. Forty-five client-owned cats diagnosed with hyperthyroidism. Cats with newly diagnosed, untreated hyperthyroidism were treated with carbimazole (5 mg PO, q12h) or methimazole (10 mg) applied to the inner pinnae q24h. Cats were examined after 0, 1, 4, 8, and 12 weeks of treatment. Clinical signs, body weight, systolic blood pressure, hematologic, serum biochemical and urine parameters, total serum thyroxine concentrations (TT4), and serum methimazole concentrations were recorded. No significant differences between groups were detected at day 0. Both formulations were effective in treating hyperthyroidism. No significant differences were detected in thyroxine concentrations, body weight, blood pressure, heart rate, alkaline phosphatase, alanine aminotransferase, creatinine, urea, and urine specific gravity (USG) between groups. The serum methimazole concentrations correlated poorly with TT4-concentrations in both groups. In this 12-week trial, once daily application of a novel formulation of transdermal methimazole applied to the pinnae was as effective and safe as twice daily oral carbimazole in the treatment of cats with hyperthyroidism. This novel formulation and transdermal application could have practical advantages to some pet owners.<sup>8</sup>

Pap A et. al. (2022), Methimazole or thiamazole is the most commonly used remedy in the medical management of hyperthyroidism, an endocrine disorder with growing prevalence, particularly in geriatric feline patients. Unfortunately, veterinarians have little, or most often, no access to the transdermal conditionings. The novelty of this research is that very few transdermal formulations that include methimazole are studied yet in the veterinary field, and most often, the efficacy of methimazole is studied using pluronic lecithin organogel or lipophilic formulations as a vehicle in healthy or hyperthyroid cats. In this aim, study followed a formulation of topical methimazole that includes a human base cream as a vehicle. Five healthy cats were included in this study and received 0.1 mL cream containing 10 mg methimazole over 15 days. The ointment was applied to the hairless portions of the inner pinna and: the body weight, hematological, biochemical parameters, the adverse effects, and total thyroxin serum concentration were monitored on day 0 and day 16. Topical reactions were observed after treatment, on day 14, after 15 days of topical methimazole application. Thyroxin serum concentration was significantly lower compared to the concentrations seen on day 0, allowing us to conclude that, the incorporation of methimazole in a dermatological cream base induces, at the same dose of 10 mg  $\times$  0.1 mL<sup>-1</sup>, a significant change in total thyroxin levels.<sup>9</sup>

### 2.4.3 Pharmacokinetics

#### Absorption

Longhofer SL et. al. (2010), Methimazole (thiamazole) is an antithyroid drug commonly used to treat feline hyperthyroidism. It is routinely given twice daily. Carbimazole is a methimazole derivative that is rapidly metabolized to methimazole in vivo. A controlled-release tablet for once-daily carbimazole therapy has recently been developed in an attempt to improve compliance during medical management of feline hyperthyroidism. The results of a crossover study in six cats suggest that the pharmacokinetics of methimazole with a single dose of this controlled-release tablet may be similar to those with a single dose of a sugar-coated methimazole tablet when the two drugs are given at an equimolar dose. The mean half-lives were nearly identical (3.12 hours, sugar-coated methimazole tablets; 3.28 hours, controlled-release carbimazole tablets). The serum concentrations of methimazole at 24 hrs were  $21.7 \pm 28.9$  ng/mL in the cats treated with 5 mg sugar-coated methimazole tablets and  $28.7 \pm 37.0$  ng/mL in the cats treated with 10 mg carbimazole tablets (which provide approximately 25% more methimazole after conversion to the active metabolite).<sup>10</sup>

Trepanier LA, et. al. (1991), the intravenous and oral disposition of the antithyroid drug methimazole was determined in 10 clinically normal cats and nine cats with naturally occurring hyperthyroidism. After intravenous administration of 5 mg methimazole, the mean residence time was significantly ( $P$  less than 0.05) shorter in the cats with hyperthyroidism than in the normal cats, but there was no significant difference between the mean values for total body clearance (CL), steady state volume of distribution ( $V_{dss}$ ), terminal elimination rate constant ( $k_e$ ), or serum terminal half-life ( $t_{1/2}$ ) in the two groups of cats. After oral administration, the mean bioavailability of methimazole was high in both the normal cats (77.6 %) and cats with hyperthyroidism (79.5 %). The values for mean residence time,  $k_e$  and serum terminal  $t_{1/2}$  after oral dosing were significantly shorter in the cats with hyperthyroidism than in the normal cats. However, after oral administration of methimazole there were no significant differences between the mean values for CL,  $V_{dss}$ , bioavailability and maximum serum concentrations or the time for maximal concentrations to be reached in the two groups of cats. Overall, most pharmacokinetic parameters for methimazole were not altered by the hyperthyroid state. However, the cats with hyperthyroidism did show a trend toward faster elimination of the drug compared with the normal cats, similar to what has been previously described for the antithyroid drug

propylthiouracil in cats. These results also indicate that methimazole is well absorbed when administered orally and has a higher bioavailability than that of propylthiouracil in cats with hyperthyroidism.<sup>11</sup>

Frenais R et. al. (2008), Carbimazole is a prodrug of methimazole is used in the treatment of hyperthyroidism in cats. The pharmacokinetics of methimazole was investigated in healthy cats following oral administration of 15 mg of carbimazole as a controlled-release tablet (Vidalta), intervet. The controlled-release tablet did not produce a pronounced concentration peak and methimazole was present in the circulation for a sustained period, compared with a conventional tablet formulation. The time to reach peak concentrations after carbimazole administration was quite long ( $T_{max}$  6 hrs). The absolute bioavailability of carbimazole was around  $88 \pm 11\%$ . Repeated oral administration daily for 13 consecutive days did not lead to accumulation of methimazole in plasma. The extent of absorption of carbimazole was about 40% higher when administered to cats that had been fed compared to fasted cats. The relative oral bioavailability of methimazole following administration of the controlled-release tablets was similar to that of a conventional release formulation ( $83 \pm 21\%$ ). The pharmacokinetics of this controlled-release formulation of carbimazole supports its use as a once daily treatment (both as a starting dose and for maintenance therapy) for cats with hyperthyroidism.<sup>12</sup>

Hill KE et. al. (2014), to determine the pharmacokinetics of a novel lipophilic formulation of transdermal methimazole compared to oral carbimazole. Healthy cats received 5 mg carbimazole orally every 12 hours for 13 treatments (N=6), then received transdermal methimazole (N=5) at a dose of 5 mg, then 10 mg, once daily on the pinna for 7 days, with 21 days between treatments. Concentrations of methimazole in serum over 24 hours and at 148 hours were determined by high performance liquid chromatography. Concentrations of methimazole in serum for the first 24 hours were not reliably detected in all cats treated with 5 mg methimazole transdermally, while for those receiving 5mg carbimazole orally and 10 mg methimazole transdermally all cats had detectable concentrations of methimazole in serum. The maximum concentration and area under the curve were lower in cats receiving 10 mg methimazole transdermally (108 (SD 25) ng/mL and 2544 (SD 216) mg. hour/mL, respectively) than those receiving 5 mg oral carbimazole (355 (SD 113) ng/mL and 31,866 (SD 439) ng. hour/mL, respectively) ( $P < 0.05$ ). The time at maximal concentration and elimination half-life were longer for 10 mg transdermal methimazole (5.2 (SD 1.1) hours and 13 (SD 3) hours, respectively) compared to 5 mg oral



carbimazole (2.1 (SD 1.6) hours and 5.1 (SD 1.2) hours, respectively). At 148 hours, mean concentrations of methimazole in serum were higher in cats receiving 10 mg methimazole transdermally (506 (SD 165) ng/mL) than for 5 mg oral carbimazole (255 (SD 28) ng/mL) or 5 mg transdermally (204 (SD 76) ng/mL). The mean relative bioavailability of 10 mg transdermal methimazole compared to oral carbimazole was 48% (min 43%, max 55%). Transdermal methimazole at a dose of 10 mg administered to the pinnae of healthy cats once daily in a novel lipophilic formulation has half the relative bioavailability compared to 5 mg oral carbimazole. Transdermal methimazole can be absorbed from the skin of healthy cats.<sup>13</sup>

Peterson ME et. al. (1993), the oral disposition of the antithyroid drugs methimazole and carbimazole were compared in nine clinically normal cats. After the administration of 5 mg of methimazole, serum concentrations of methimazole increased in all the cats, with mean drug concentrations reaching peak values (1.37 µg/ml) at 30 minutes. After administration of 5 mg carbimazole, serum concentrations of carbimazole remained low, but serum methimazole became readily measurable, with mean drug concentrations reaching peak values (0.79 µg/ml) at 120 minutes. When serum concentrations of methimazole attained after administration of the two anti-thyroid drugs were compared, the mean maximum serum methimazole concentration achieved after administration of methimazole was approximately two-fold higher than peak concentrations measured after administration of carbimazole. In addition, the mean area under the serum concentration curve (AUC) after administration of methimazole was approximately two fold higher than the mean AUC determined after administration of carbimazole. When the difference in molecular weight between the two drugs was taken into consideration, however, these methimazole: carbimazole ratio of 2:1 were nearly equivalent to the molar ratio of the 5 mg doses of the drugs given (1.63). Results of this study indicate that carbimazole is nearly totally converted to methimazole after oral administration to cats, similarly to the findings in man. The finding of less available serum methimazole after administration of a 5 mg tablet of carbimazole than after methimazole is also consistent with published antithyroid drug dosages needed to control hyperthyroidism in cats.<sup>14</sup>

Trepanier L.A. et. al. (1991), Pharmacokinetics of intravenous and oral methimazole following single and multiple-dose administration in normal cats. The pharmacokinetics of methimazole (MMI) administered intravenously and orally was determined in six adult domestic short haired cats. There was no significant difference between mean serum MMI concentrations after oral and i.v. administration by 30 min post-MMI administration, indicating relatively rapid and complete

absorption of the drug. The bioavailability of MMI ranged from 27% to 100% (mean =  $81.1 \pm 11.4\%$ ). The mean serum elimination half-life was  $6.6 \pm 2.0$  h, with a wide range of values (1.9 h-15.1 h). After repeat i.v. administration of MMI following 2 weeks of oral administration of the drug, no significant difference was found between mean serum concentrations after single-dose and multiple-dose administration. No significant change in serum elimination half-life or total body clearance was found after multiple-dose administration of MMI. Two cats with the longest half-lives (9.9 h and 15.1 h), however, did exhibit markedly shorter  $t_{1/2}$  values (3.5 h and 3.3 h, respectively) after multiple-dose administration. Values for central and steady state volumes of distribution also decreased after multiple-dose administration, possibly indicating saturation of thyroid uptake of MMI with chronic administration. These results indicate that MMI has good oral bioavailability and has a longer mean serum elimination half-life than propylthiouracil, the other anti-thyroid drug that has been evaluated in cats. Although, no significant change in mean values occurred after multiple-dose administration of MMI, drug-induced acceleration of metabolism may occur in some cats after long-term MMI administration.<sup>15</sup>

### Distribution

Pittman JA et. al. (1971), the results of the studies with MMI-2-<sup>14</sup>C are shown in below table. About three fourths of the radioactivity appeared in the urine over the four days of study, while fecal excretion accounted for only 6.4% of the dose. The total recovered was 90.4% of the administered dose; no attempt was made at total recovery by carcass analysis. All organs contained total quantities less than 1 % of the administered dose except the liver (2.14%) and small intestine (1.43%). When the tissue concentrations were expressed as organ/plasma (O/P) ratios, the thyroid and adrenal glands had much higher concentrations of radioactivity than other tissues.<sup>16</sup>

TABLE 1. Urinary and fecal excretion of radioactivity following intravenous administration of MMI-2-<sup>14</sup>C to rats

Source	% of dose (means $\pm$ SEM)
Urine, Day 1	$69.52 \pm 2.25$
Urine, Day 2	$3.37 \pm 0.70$
Urine, Day 3	$1.88 \pm 0.59$
Urine, Day 4	$1.60 \pm 0.50$
Total	$76.37 \pm 1.49$
Feces, Day 1	$4.20 \pm 0.95$
Feces, Day 2	$1.10 \pm 0.37$
Feces, Day 3	$0.72 \pm 0.30$
Feces, Day 4	$0.34 \pm 0.14$
Total	$6.36 \pm 1.42$

TABLE 2. Tissue distribution and organ/plasma (O/P) ratios of radioactivity in rats four days after administration of MMI-2-<sup>14</sup>C

Organ	Concentration of radioactivity (expressed as parent compound $\mu$ moles/g, mean $\pm$ SEM)	O/P ratio
Thyroid	$2.23 \pm 0.21$	$129 \pm 42$
Adrenals	$1.72 \pm 0.81$	$117 \pm 68$
Thymus	$0.45 \pm 0.01$	$25 \pm 6.8$
Diaphragm	$0.36 \pm 0.07$	$21.7 \pm 8.7$
Kidney	$0.24 \pm 0.08$	$15.3 \pm 7.8$
Brain	$0.13 \pm 0.09$	$8.5 \pm 3.5$
Liver	$0.13 \pm 0.03$	$8.0 \pm 3.6$
Colon	$0.14 \pm 0.05$	$6.3 \pm 0.8$
Testes	$0.11 \pm 0.007$	$6.2 \pm 1.8$
Small intestine	$0.08 \pm 0.007$	$4.4 \pm 1.3$
Stomach	$0.08 \pm 0.02$	$3.5 \pm 0.28$
Plasma	$0.021 \pm 0.002$	—

Skellern GG et. al. (1973), in distribution studies a significant proportion of total whole blood radioactivity was located in the cells. Similar uptake of other thioamide compounds has been reported. With  $^{35}\text{S}$ -methimazole 40% of blood radioactivity was associated with the blood cells. With  $^{14}\text{C}$ -methimazole, but not  $^{35}\text{S}$ -methimazole, a slight concentration gradient between blood cells and plasma appeared at 4 to 5 days; rapid uptake of  $^{14}\text{C}$ -methimazole by blood cells is in accord with a moderate lipid affinity of methimazole. Sulphonamides have been found in blood cells several days after administration although not present in plasma.<sup>17</sup>

The concentration of radioactivity in the thyroid is greater than in any other tissue; the thyroid/plasma ratio was 62.5 at 4 days. Giving 25 mg/kg of  $[2\text{-}^{14}\text{C}]$ methimazole intravenously, found a thyroid/plasma ratio of 129 at 4 days, whilst rats receiving 0.54 mg/kg of  $^{35}\text{S}$ -methimazole intraperitoneally had a ratio of 838 at 4 days.<sup>17</sup>

Distribution of radioactivity in the female rat 24 h after injection of  $^{14}\text{C}$ -methimazole was similar to that in males, except that uptake of radioactivity by the thyroid was about 30% lower.<sup>17</sup>

### **Metabolism**

Lee PW et. al. (1978), the incubation of methimazole (1-methyl-2-thioimidazole, MMI) with rat hepatic microsomes led to the formation of 3-methyl-2-thiohydantoin and N-methylimidazole. In addition, an NADPH-stimulated binding of  $^{14}\text{C}$  and  $^{35}\text{S}$  from  $[^{14}\text{C}]$ - and  $[^{35}\text{S}]$ MMI to microsomal macromolecules was seen. Both the NADPH-stimulated N-methylimidazole formation and binding of radioactivity from  $[^{14}\text{C}]$ - and  $[^{35}\text{S}]$ MMI to microsomal macromolecules appeared to be catalyzed largely by the cytochrome P-450 to monooxygenase systems of rat hepatic microsomes. A portion of the radioactivity bound to microsomes incubated with  $[^{14}\text{C}]$ - and  $[^{35}\text{S}]$ MMI was released as unchanged MMI on prolonged incubation under acid conditions; this suggests that strong binding of MMI to microsomes occurred. A portion of the  $^{35}\text{S}$  bound to microsomes incubated with  $[^{35}\text{S}]$ MMI can be released as  $^{35}\text{SCN}^-$  on incubation of the  $^{35}\text{S}$ -labeled microsomes with  $\text{CN}^-$ . These data suggest that a portion of the sulfur released in the metabolism of MMI to N-methylimidazole is in the form of atomic sulfur (S), which binds to cysteine sulfhydryl groups (R-S-H) in microsomal proteins to form a hydrodisulfide (R-S-S-H).<sup>18</sup>

Skellern GG et. al. (1981), After intraperitoneal administration of  $[2\text{-}^{14}\text{C}]$ methimazole to rats, the radioactivity is rapidly and appreciably eliminated in the urine and that methimazole is extensively metabolized, since only 6.7 % of the dose is excreted unchanged. Almost complete recoveries of radioactivity were obtained after extraction with chloroform and n-butanol of the

control urine to which [2-<sup>14</sup>C]methimazole had been added, while 47.5% of the <sup>14</sup>C administered to the rats remained in the urine after similar extractions, indicating the metabolism of [2-<sup>14</sup>C]methimazole to more polar metabolites.<sup>19</sup>

*N*-Methylimidazole, a known metabolite of methimazole *in-vitro*, is thought to be formed by the initial oxidation of the sulphur atom in methimazole to the sulphenic acid, followed by further oxidation to the sulphinic acid which is subsequently hydrolysed. These oxidation reactions have been shown to be catalysed by a hepatic microsomal flavoprotein mixed-function oxidase which is dependent on NADPH and molecular oxygen, and is present in a variety of tissues and species including rat.<sup>19</sup>

*N*-Methylimidazole could also be a proximate metabolite of the methylhydantoin, as it has been reported that [<sup>14</sup>C] imidazole is metabolized to [<sup>14</sup>C]hydantoin in the rat.<sup>19</sup>

### **Elimination**

Hill KE et. al. (2015), there are no significant differences between the pharmacokinetics of methimazole and carbimazole in cats. The serum half- life (measured as methimazole) after oral administration of 5 mg of carbimazole was 4.4 hours and after administration of 5 mg of methimazole between four to six hours. In hyperthyroid cats, there is a trend for faster elimination of methimazole, however this more rapid elimination is not considered important in regard to therapy.<sup>7</sup>

Trepanier LA et. al. (1991), Pharmacokinetics of intravenous and oral methimazole following single and multiple-dose administration in normal cats. The pharmacokinetics of methimazole (MMI) administered intravenously and orally was determined in six adult domestic short haired cats. The mean serum elimination half-life was  $6.6 \pm 2.0$  h, with a wide range of values (1.9 h- 15.1 h). No significant change in serum elimination half-life or total body clearance was found after multiple-dose administration of MMI. Two cats with the longest half-lives (9.9 h and 15.1 h), however, did exhibit markedly shorter  $t_{1/2}$  values (3.5 h and 3.3 h, respectively) after multiple-dose administration. Values for central and steady state volumes of distribution also decreased after multiple-dose administration, possibly indicating saturation of thyroid uptake of MMI with chronic administration. These results indicate that MMI has good oral bioavailability and has a longer mean serum elimination half-life than propylthiouracil, the other anti-thyroid drug that has been evaluated in cats. Although, no significant change in mean values occurred after

multiple-dose administration of MMI, drug-induced acceleration of metabolism may occur in some cats after long-term MMI administration.<sup>15</sup>

### **Pharmacokinetic drug interactions**

López-García ML et. al. (1998), the influence of methimazole (MTZ) inhibitor of the microsomal oxidases on the systemic availability of the albendazole sulpho-metabolites (ABZS-MT) albendazole-sulphoxide (ABZSO) and albendazole-sulphone (ABZSO<sub>2</sub>) and on its anthelmintic effects was investigated in a mouse model for helminthic infections. Plasma concentrations of the ABZS-MT were measured by high performance liquid chromatography (HPLC) following treatment of Swiss CD-1 mice with albendazole (ABZ) alone or ABZ plus MTZ, at both single and repeated doses. The anthelmintic effects were assessed in age-matched mice similarly treated following infection with *Trichinella spiralis*. MTZ significantly ( $p < 0.01$ ) increased the ABZS-MT plasma concentrations although the pharmacokinetic profile varied greatly according to the dose of ABZ administered. When ABZ was given at a single dose of 50 mg/kg followed by MTZ at 3 mg/kg, a cumulative effect was observed in the ABZS-MT plasma levels with pharmacokinetic parameters ( $T_{max} = 24$  h,  $C_{max} = 30.88$  µg/ml and  $AUC = 1120.80$  µg h/ml) significantly ( $p < 0.01$ ) higher than those following administration of ABZ alone ( $T_{max} = 3$  h,  $C_{max} = 11.00$  microg/ml and  $AUC = 268.03$  µg h/ml). This cumulative effect was absent following administration of ABZ at 100 mg/kg where, after reaching a maximum ( $C_{max} = 27.23$  µg/ml) at 3 h post-administration ( $T_{max}$ ), the ABZS-MT plasma levels fell down quickly to values under those obtained after administration of ABZ at the same dose, but alone ( $AUC = 362.15$  µg h/ml vs.  $340.15$  µg h/ml, respectively). When ABZ was given at 50 mg/kg together with MTZ three times every 24 h, a rapid decrease was observed in the ABZS-MT plasma levels following administration of both the second and third doses, respectively. The pharmacokinetic profile of ABZS-MT following administration of each of the three doses of ABZ at 100 mg/kg plus MTZ was the same as that obtained after the single treatment. The rapid decrease of the ABZS-MT plasma levels observed after the sustained treatment or after the single treatment at 100 mg/kg could be due to a microsomal oxidase inductive effect (probably the cytochrome P-450) caused by ABZSO. The co-administration of MTZ significantly ( $p < 0.01$ ) increased the anthelmintic effects of ABZ against both migrating and encysted larvae of *T. spiralis*.<sup>20</sup>

Lanusse CE et. al. (1992), A zwitterion suspension of NTB was given orally at 7.5 mg/kg to sheep either alone (control treatment) or co-administered with methimazole (MTZ) orally (NTB

+ MTZ oral treatment) or intra-muscularly (NTB + MTZ i.m.) at 3 mg/kg. Blood samples were taken serially over a 72 h period and plasma was analysed. Only trace amounts of NTB parent drug and ABZ were detected in the earliest samples after either treatment. There were significant modifications to the disposition kinetics of ABZSO in the presence of MTZ. ABZSO elimination half-life increased from 7.27 h (control treatment) to 14.57 h (NTB + MTZ oral) and to 11.39 h (NTB + MTZ i.m.). ABZSO AUCs were significantly higher ( $P$  less than 0.05) for the NTB + MTZ oral treatment (+55%) and for the NTB + MTZ i.m. treatment (+61%), compared with the NTB alone treatment. The mean residence times for ABZSO were 12.66  $\pm$  0.68 h (control treatment), 18.85  $\pm$  2.35 h (NTB + MTZ oral) and 17.02  $\pm$  0.90 h (NTB + MTZ i.m.). There were no major changes in the overall pharmacokinetics of ABZSO<sub>2</sub> for the concomitant MTZ treatments. However, delayed appearance of this metabolite in the plasma resulted in longer ABZSO<sub>2</sub> lag times and a delayed  $T_{\max}$  for treatments with MTZ.<sup>21</sup>

Lanusse CE et. al. (1995), the influence of methimazole on the plasma disposition kinetics of fenbendazole, oxfendazole and their metabolites, was investigated in adult sheep. The two anthelmintics were administered by oral drench at 5 mg kg<sup>-1</sup> either alone (control treatments) or together with methimazole given orally at 3 mg kg<sup>-1</sup>. Blood samples were taken serially for 144 hours. The disposition of each analyte followed a similar pattern after the administration of the two anthelmintics alone. Oxfendazole was the main component recovered in plasma between four and 120 to 144 hours after the administration of both anthelmintics either with or without methimazole. A modified pattern of disposition, with significantly higher  $C_{\max}$  and AUC values for fenbendazole parent drug, and a delayed appearance in plasma with retarded  $T_{\max}$  values for the sulphoxide and sulphone metabolites, were the main pharmacokinetic changes observed when the drugs were administered with methimazole.<sup>22</sup>



## 2.4.4 Toxicology

### 2.4.4.1 Acute toxicity

Acute LD50 values for Methimazole after different routes of exposure in mouse and rat are LD50 Rat oral 2250 mg/kg, LD50 Rat sc 1050 mg/kg, LD50 Mouse oral 860 mg/kg, LD50 Mouse ip 500 mg/kg and LD50 Mouse sc 345 mg/kg.<sup>23</sup>

### 2.4.4.2 Repeated-dose toxicity

Nambiar PR et. al. (2014), Thionamides such as propylthiouracil (PTU) and methimazole (MMI) have been used for more than 50 years to treat the more common causes of thyrotoxicosis/hyperthyroidism such as Graves' disease. Serious adverse effects associated with thionamides in humans include idiosyncratic liver damage, agranulocytosis, aplastic anemia, and vasculitis. Both prospective and retrospective clinical studies with these drugs have failed to identify predictive biomarker for these adverse effects. To assess whether rat is a good model for predicting drug-related adverse events in the liver and in the bone marrow, we conducted a comprehensive study in male rats with multiple doses of PTU and MMI. As expected, euthyroid animals became hypothyroid along with several secondary changes associated with hypothyroidism. There were slight reductions in red blood cell parameters along with some marginal effects on the bone marrow elements. However, there was no evidence of significant neutropenia and liver injury in both PTU-treated and MMI-treated cohorts. MMI-related effects were noted in the seminiferous tubules of the testes. Overall, 1-month daily treatment of euthyroid rats with PTU or MMI resulted in hypothyroidism, minor bone marrow effects, and several secondary effects associated with hypothyroidism, but without any evidence of adverse effects reported in humans including liver injury and agranulocytosis.<sup>24</sup>

### 2.4.4.3 Genotoxicity

No literature data is available to describe the potential *Mutagenicity/genotoxicity* effects of Carbimazole. Carbimazole is been safely used since from 1995 and currently there is no apparent sign and reporting of *Mutagenicity/genotoxicity* effect with Carbimazole. However the potential for carcinogenic risk from the chronic use of Carbimazole is unknown.

### 2.4.4.4 Carcinogenicity

Mallela MK et. al. (2014), propylthiouracil (PTU) and methimazole (MMI) are anti-thyroid drugs used to treat hyperthyroidism. Despite the widespread use of PTU and MMI during pregnancy, modest clinical data and little animal data are available on the teratogenic potential of

these drugs. Pregnant C57Bl/6 mice were treated daily with PTU (10 mg/kg or 100 mg/kg), MMI (2 mg/kg or 20 mg/kg), or vehicle from gestation day (GD) 6–16. GD 18 fetuses were evaluated for gross and histopathological abnormalities. Next, pregnant Sprague-Dawley rats were treated daily with PTU (50 mg/kg or 100 mg/kg), MMI (10 mg/kg or 20 mg/kg) or vehicle from GD 6–19, followed by evaluation for gross and histopathological abnormalities at GD 20. In mice treated with PTU or MMI, no significant histopathological abnormalities or external gross malformations, and no adverse effects on placental weight, litter size, resorption rates, or fetal weight were observed at GD18. In rats, no adverse effects on litter size, placental weights, or maternal body weights were observed with either PTU- or MMI- treatment. PTU (50 mg/kg and 100 mg/kg), and MMI (10 mg/kg) treatment resulted in a decrease in crown-rump length in rat fetuses but no external gross malformations or histopathological abnormalities were observed. They did not observe either gross external malformations or histopathological malformations in mice or rats treated long-term with high doses of PTU or MMI during pregnancy. Considering these data along with human epidemiological data, author are moving to a more clear understanding of the risks of these drugs during pregnancy. Collectively, these data suggest that if there is a risk of either PTU or MMI on the developing embryo, these risks are very small. Furthermore, there is little support for the notion that MMI is teratogenic whereas PTU is not.<sup>25</sup>

Owen NV et. al. (1973), Harlan rats were fed methimazole in the diet at levels of 0, 5, 30 and 180 ppm for 2 yr. Survival was poor in the rats of the 180 ppm group and their growth was greatly retarded. Hypertrophy and hyperplasia of the thyroid occurred in rats of the 30 and 180 ppm groups but not in those of the 5 ppm group. In rats of the 30 and 180 ppm groups there was a high incidence of thyroid follicular adenoma and a lower incidence of follicular adenocarcinoma. A follicular adenoma was also found in one rat of the control group and one given 5 ppm methimazole, while one rat in the control group had a follicular adenocarcinoma. Incidence and induction time of neoplasias other than of the thyroid were similar in the treated and control groups. The no-effect dietary level of methimazole on the thyroids of rats was found to be 5 ppm.<sup>26</sup>

#### **2.4.4.5 Reproductive and developmental toxicity**

Comer CP et. al. (1982), Postnatal neurological development was evaluated in the offspring of groups of eight Sprague-Dawley rats given drinking-water containing methimazole at a concentration of 0 or 0.1 g/L from day 17 of gestation to postnatal day 10. The growth of offspring was reduced relative to that of controls after postnatal day 2, and they showed



significant delays in acquisition of the surface-righting response (at 14 days vs 7 days in controls), auditory startle reflex (at 18 vs 12 days) and eye opening (at 17 vs 15 days). They also showed a significant reduction in locomotor activity in a 10-min open-field test at 21 days.<sup>27</sup>

Stanisstreet M et. al. (1990), a literature review of individual pregnancies and recent surveys involving large cohorts reveal an association between congenital malformation and maternal hyperthyroidism, suggesting that some aspect of hyperthyroidism or its treatment might compromise the development of the fetus. Experiments have shown that the thyroid antagonist, ethylenethiourea (ETU), causes fetal malformations when administered to pregnant rats, but it is not known whether it is ETU or the imbalance in maternal thyroid hormone which it causes which is the teratogenic agent. Here we employ in vitro culture to determine the possible direct effects on rat embryos of two thyroid antagonists, ETU and methimazole (MMI), the latter being one which is used for treatment of thyrotoxicosis in humans. It was found that ETU can compromise the development of rat embryos in vitro, confirming that ETU has a direct effect on the rat embryo. It was also found that MMI can cause abnormal development of rat embryos in vitro, although the concentration at which MMI disturbs rat embryogenesis is higher than that which is reached in hyperthyroid patients treated with clinical doses of MMI or carbimazole.<sup>28</sup>

Khan AR et. al. (2013), in the study the teratogenic and embryotoxic effects of Neomercazole was studied in Albino mice during organogenesis. The dose groups used were 0.2, 0.4, 0.6 and 0.8 µg/gBW. The pregnant mice were exposed to these dose groups on days 8 and 12 of gestation. Fetuses were recovered on day 18 of gestation and were subjected to morphological, morphometric and skeletal studies. Morphological studies revealed anomalies like distorted axis, hydrocephaly, microphthalmia, open eye lid, agnathia, micromelia, syndactyly, subcutaneous hemorrhages and kinky tail. Moreover, there was overall decline in litter size and upsurge in percentage of fetal resorptions. Detailed study of skeletal parameter presented reduction in ossification in skull, ribs and limb region.<sup>29</sup>

Rice SA et. al. (1987), Methimazole was tested for use as a positive control agent in behavioral studies of mice. Continuous administration of the antithyroid agent via drinking water (0.1 mg/mL) from day 16 of pregnancy through day 10 postpartum produced developmental delays in mouse offspring. Ten methimazole and 12 untreated litters were studied. Developmental milestones were unaltered; ie, time of pinna detachment, incisor eruption, eye opening, vaginal patency, and testicular descent were not different between groups. Mean body weights of methimazole offspring were consistently reduced, but significant differences were isolated to a

few days in the preweaning period and a few weeks during the postweaning period. There was no enduring effect. All preweaning tests showed some significant treatment-related changes; methimazole pups were developmentally delayed. Surface righting time was increased while time pivoting and the number of quadrants traveled were decreased in methimazole pups. Negative geotaxis showed significant treatment-related increases in the time to orient 180 deg uphill, the percentage of pups orienting 180 deg uphill, and the percentage of pups orienting < 180 deg. Ontogeny of swimming ability also showed significant delays. The only postweaning test evaluated, time on a rotating rod, showed no treatment-related effects. Brain weights on postnatal day 120 were not different between groups.<sup>30</sup>

Ramhøj L et. al. (2022), Exposure of pregnant rat dams to MMI or amitrole during gestation and lactation decreased dam weight gain during pregnancy but did not change gestational length, litter size, pup survival or early postnatal maternal weight gain. Additionally, pup birth weight was reduced in both sexes when exposed to 16 mg/kg MMI and in female pups exposed to 50 mg/kg amitrole. Offspring body weights and weight gains were reduced by high dose MMI and amitrole throughout the postnatal period. Except for male pup PD6 weights and weight gain PD614, that were decreased by 8 mg/kg MMI, there were no effects on body weights or weight gains in the low dose groups. Apart from the reduced body weights and growth there were no other signs of overt toxicity in dams or pups. Liver weights in PD22 dams and PD16/17 offspring were nominally smaller, probably as a consequence of reduced body weights as there were no effects on liver weights relative to body weight.<sup>31</sup>

#### **2.4.4.6 Other toxicity studies**

Vail DM et. al. (1993), the protective effect of methimazole, a commonly used antithyroid drug, on cisplatin-induced nephrotoxicity was studied. Eight dogs received 80 mg/m<sup>2</sup> cisplatin i.v. without saline prehydration. Dogs were randomized into two groups of four dogs each: one group received 40 mg/kg methimazole i.p. at 30 min prior to and 4 h after cisplatin delivery, and the other group received saline placebo i.p. Methimazole protected dogs against the in vivo nephrotoxicity elicited by cisplatin as evidenced by clinicopathologic and histopathologic indices. Protection was not complete, as methimazole-treated animals developed mild histopathologic renal changes. Measures of renal oxidative stress did not differ between the two groups at day 5 following cisplatin treatment. No difference was noted for serum thyroxine concentrations before or after therapy in either group; however, serum levels of 3,5,3'-triiodothyronine were significantly higher on day 5 in both groups of dogs receiving cisplatin,

regardless of whether they received methimazole or not. Methimazole as used in this study was found to be well tolerated in dogs over the short term, with no significant clinical or clinicopathologic toxicity being observed. The results of this study support the additional evaluation of methimazole as a protectant against cisplatin-induced nephrotoxicity using the dog as a model.<sup>32</sup>

Based on the data submitted, it is estimated from the product ingredients that Vidalta 15 mg Tablets for Cats (66165) and Vidalta 10 mg Tablets for Cats (66168) have low acute oral, dermal and inhalation toxicity, and are not a skin or eye irritant or a skin sensitizer. Adverse effects associated with drugs that suppress thyroid hormone secretion have been seen in hyperthyroid patients receiving the active ingredient (carbimazole and methimazole). Chronic toxicity studies in rats and mice indicate that the thyroid gland is the primary target organ with thyroid tumours observed, though these are considered to be of limited relevance to humans. No reliable evidence of a genotoxic potential for methimazole has been seen in vitro or in vivo from the limited data. Developmental toxicity and developmental neurotoxicity have been observed in animal studies following administration of methimazole over the gestation and/or lactation period. Additionally, developmental toxicity was seen in a child from a hyperthyroid patient who received methimazole during pregnancy. No standard reproductive toxicity or neurotoxicity studies in experimental animals are available.<sup>33</sup>

Akmal A et. al. (2014), Propylthiouracil (PTU) has been used for the treatment of hyperthyroidism since the 1940s, but over the years reports of significant hepatotoxicity have come forth, particularly in children. This led to a black box warning being issued by the USFDA in 2009, followed by a similar warning by the European Medicines Agency and the United Kingdom Medicines and Healthcare Regulatory Agency later that year. This article provides a concise review of the data on hepatotoxicity associated with the currently available antithyroid drugs: PTU, methimazole (MMI) and carbimazole. The differences in mechanism are examined in detail, as well as clinical presentation, management and monitoring. Use in special populations and trends in use of antithyroid medication are also discussed. PTU is known to cause severe hepatic failure, particularly in children. Its use in children should be avoided. In adults, it is beneficial to use in the first trimester of pregnancy and thyroid storm. In the rest of the adult population, it should be used with caution. Carbimazole and MMI are associated with less severe hepatic injury and should be preferred when choosing thionamides as a treatment option.<sup>34</sup>

Genter MB et. al. (1995), Methimazole was toxic to the olfactory system in Long-Evans rats given a single intraperitoneal dose of  $\geq 25$  mg/kg bw or an oral dose of  $\geq 50$  mg/kg bw. A300-mg/kg bw intraperitoneal dose resulted in almost complete destruction of the olfactory epithelium.<sup>35</sup>

#### **Environmental Risk Assessment:**

Directive 2001/83/EC as amended requires the applicant of a marketing authorization for a medicinal product for human use to evaluate any potential risks of the medicinal product to the environment.

The current application of medicinal product Carbimazole 10 mg and 15 mg Tablets is a hybrid application which comes under Regulation 52B of the Human Medicines Regulations 2012, as amended [previously Article 10(3) of Directive 2001/83/EC, as amended]. Flamingo Pharmaceutical Limited, India develops generic products Carbimazole 10 mg and 15 mg Tablets, the generic application claiming essential similarity with the reference product NeoMercazole 20 mg Tablets, MAH- Amdipharm Limited, Ireland.

In view of this current application being a generic medicinal product, an in depth environment risk assessment has not been performed (section 8 of the guidance document no. EMEA/CHMP/SWP/4447/00 Rev. 1 i.e. Guideline on the environmental risk assessment of medicinal products for human use). Since, Carbimazole 10 mg and 15 mg Tablets is generic medicinal products, the possibility of risks to the environment from the point of their use are expected to be the same as those of the reference product.

It is expected that once authorized, this generic version of carbimazole 10 mg and 15 mg Tablets will be prescribed as an alternative to the current branded product or other generic products. The availability of this generic carbimazole product is unlikely to have an impact on the total prescribed amount of carbimazole. The environmental risk associated with the approval and marketing of this product will therefore be negligible.

## 2.4.5 Integrated Overview and Conclusions

### Pharmacology:

Carbimazole is a thyroid reducing agent or antithyroid agent. The products are indicated in conditions where reduction of thyroid function is required, including, hyperthyroidism, preparation for thyroidectomy in hyperthyroidism and as therapy prior to and post radio-iodine treatment. The method of action of carbimazole 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.

### Pharmacokinetics:

The controlled-release tablet did not produce a pronounced concentration peak and methimazole was present in the circulation for a sustained period, compared with a conventional tablet formulation. The time to reach peak concentrations after carbimazole administration was quite long ( $t_{\max}$  6h). The absolute bioavailability of carbimazole was around  $88 \pm 11\%$ . Repeated oral administration daily for 13 consecutive days did not lead to accumulation of methimazole in plasma. The extent of absorption of carbimazole was about 40% higher when administered to cats that had been fed compared to fasted cats. The relative oral bioavailability of methimazole following administration of the controlled-release tablets was similar to that of a conventional release formulation ( $83 \pm 21\%$ ). Two cats with the longest half-lives (9.9 hr and 15.1 hr), however, did exhibit markedly shorter  $t_{1/2}$  values (3.5 hr and 3.3 hr, respectively) after multiple-dose administration. Values for central and steady state volumes of distribution also decreased after multiple-dose administration, possibly indicating saturation of thyroid uptake of MMI with chronic administration. These results indicate that MMI has good oral bioavailability and has a longer mean serum elimination half-life than propylthiouracil, the other anti-thyroid drug that has been evaluated in cats.

### Toxicology:

Chronic toxicity studies in rats and mice indicate that the thyroid gland is the primary target organ with thyroid tumours observed, though these are considered to be of limited relevance to humans. No reliable evidence of a genotoxic potential for methimazole has been seen in vitro or in vivo from the limited data. Developmental toxicity and developmental neurotoxicity have

been observed in animal studies following administration of methimazole over the gestation and/or lactation period. Additionally, developmental toxicity was seen in a child from a hyperthyroid patient who received methimazole during pregnancy.

## 2.4.6 Impurities

### Drug substance:

The active substance manufacturer, [REDACTED]

The copy of current [REDACTED]

The [REDACTED]

[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]

The limits of related substances and residual solvents present in the drug substance are in compliance with ICH Q3A(R2).

### Drug Product:

The following related substance limits are proposed for the finished product:

Related substances	[REDACTED]
Thiamazole	[REDACTED]
Any secondary peak	[REDACTED]
Total Impurities	[REDACTED]

The limits of related substances present in the drug product are in compliance with ICH Q3B(R2) and in line with BP monograph.

The composition of the Carbimazole 10 mg and 15 mg Tablets is as follows:

Ingredients/Grade	Function	Specification	Quantity/Tablet (mg)		% w/w
			10 mg Tablets	15 mg Tablets	
Carbimazole	Active Ingredient	Ph. Eur.			
Lactose Monohydrate	Diluent	Ph. Eur.			
Microcrystalline Cellulose (PH – 102)	Diluent and Binder	Ph. Eur.			
Citric Acid Monohydrate	Buffering agent and pH Modifier	Ph. Eur.			
Sucrose	Binder	Ph. Eur.			
Ferric oxide (Red)	Colorant	USP/NF			
Magnesium Stearate	Lubricant	Ph. Eur.			5
Average weight of Tablet					

These excipients used in the drug product are widely used in oral pharmaceutical products and all excipients are compendial (Ph. Eur./USP-NF), refer to the [Section 3.2.P.1](#) for details.

None of the above excipient used in the manufacture of Carbimazole 10 mg and 15 mg Tablets, is of animal origin except lactose monohydrate and this has been addressed in [Section 3.2.A.2](#).

The [TSE/BSE and GMO Free certificates](#) for all the excipients are enclosed in Section 3.2.P.4.5.



### Elemental Impurity

Based on ICH Q3D, a risk assessment was carried out to evaluate the probability of elemental impurities in the Carbimazole 10 mg and 15 mg Tablets and to establish the appropriate controls to ensure the quality of the drug product.

Potential risks	Action/mitigation
Elemental impurities from drug substance & excipients	No action required; Controls sufficient
Elemental impurities from equipment	
Elemental impurities from container closure systems	No action required, negligible risk

The risk assessment for elemental impurities in Carbimazole 10 mg and 15 mg Tablets can be concluded by considering that the observed values are within the drug product control strategy.

The components risk approach for maximum daily intake of each component is found within control threshold of 30% of PDEs of elemental impurities. Elemental impurities observed are within the control threshold.

Risk assessment has been conducted to evaluate the presence of elemental impurities in Carbimazole 10 mg and 15 mg Tablets, in-line with the requirements of the ICH Q3D guideline (EMA/CHMP/ICH/353369/2013) and the detailed report of [Elemental impurities risk assessment](#) as per ICH Q3D is enclosed in Section 3.2.P.5.5.

### Nitrosamine Impurities

The applicant has evaluated the risk of the presence of nitrosamine impurities in the finished product in accordance with the recently published Article 5(3) Referral on Nitrosamines. The [Nitrosamine risk assessment summary](#) is enclosed in section 3.2.P.5.5.

#### 2.4.7 List of Literature Citations

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