



**Veterinary
Medicines
Directorate**

**United Kingdom
Veterinary Medicines Directorate
Woodham Lane
New Haw
Addlestone
Surrey KT15 3LS**

MUTUAL RECOGNITION PROCEDURE

**PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY
MEDICINAL PRODUCT**

**Vidalta 10 mg prolonged- release tablets for cats
Vidalta Vet 10 mg prolonged-release tablets for cats
(BE, NO)**

**Vidalta 15 mg prolonged- release tablets for cats
Vidalta Vet 15 mg prolonged-release tablets for cats
(BE, NO)**

**PuAR correct as of 27/03/2018 when RMS was transferred
to IE. Please contact the RMS for future updates**

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0408/001/MR UK/V/0408/002/MR
Name, strength and pharmaceutical form	Vidalta 10 mg prolonged-release tablets for cats Vidalta 15 mg prolonged-release tablets for cats
Applicant	Intervet UK Ltd Walton Manor Walton Milton Keynes Buckinghamshire MK7 7AJ
Active substance(s)	Carbimazole
ATC Vetcode	QH03BB01
Target species	Cats
Indication for use	Treatment of hyperthyroidism and hyperthyroidism-associated clinical signs in cats.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies (veterinary) (HMA(v)) website (www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Applications in accordance with Article 12(3) of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	26 October 2011
Date product first authorised in the Reference Member State (MRP only)	21 December 2007
Concerned Member States for original procedure	Austria Belgium Bulgaria Cyprus Denmark France Germany Greece Hungary Ireland Italy Luxembourg Malta The Netherlands Norway Poland Portugal Romania Spain

I. SCIENTIFIC OVERVIEW

Vidalta 10 mg prolonged-release tablets for cats and Vidalta 15 mg prolonged-release tablets for cats contain the active substance carbimazole. These products are indicated for the treatment of hyperthyroidism and hyperthyroidism-associated clinical signs in cats. Carbimazole belongs to the family of mercaptoimidazoles and is the pro-drug¹ of methimazole which depresses thyroid function by inhibiting thyroid peroxidase, needed for the synthesis of thyroid hormones.

Feline hyperthyroidism, if untreated, is invariably fatal as a consequence of the cardiac failure it induces. Currently the treatment options in the UK for cats with hyperthyroidism are radioactive iodine therapy, (which has limited availability), surgical thyroidectomy, or medical treatment with methimazole tablets. Surgery may not be a viable option for high-risk patients with intercurrent disease. Medical therapy is commonplace and these products offer an advantage for compliance as the prolonged release formulation requires only once daily administration. The starting dose is one 15 mg tablet per cat. The dose is then adjusted according to the clinical and hormonal response. In stabilised cats, the therapeutic dose ranges between 10 mg and 25 mg, once daily. A lower dose (every other day dosing) may be required in a few cases.

These applications were submitted in accordance with Article 12 (3) of Directive 2001/82/EC, as amended. These products were first authorised in the UK in December 2007.

The products are manufactured and controlled using validated methods and tests which ensure the consistency of the product released on the market. It has been shown that the products can be safely used in the target species; the slight reactions observed are indicated in the SPC. The products are safe for the user and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC². The efficacy of the products was demonstrated according to the claims made in the SPC. The overall benefit/risk analysis is in favour of granting a marketing authorisation.

¹ A pro-drug is a drug substance which is administered in an inactive (or significantly less active) form. Once administered, the prodrug is metabolised in vivo into an active metabolite

² SPC - Summary of Product Characteristics

II. QUALITY ASPECTS

A. Composition

The products contain carbimazole as an active substance and excipients hypromellose, microcrystalline cellulose, red ferric oxide (E172), silica colloidal anhydrous, magnesium stearate and talc.

The products are packaged in high density polyethylene containers of 30 or 100 tablets, closed with a polypropylene tamper-evident child-resistant screw cap bearing a desiccant. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation is justified.

B. Method of Preparation of the Product

The products are manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site.

Process validation data on the product have been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substance carbimazole is an established active substance which is described in the European Pharmacopoeia (Ph. Eur.). Supporting data have been provided in the form of European Drug Master File (EDMF). It is considered that the manufacturing process is adequately controlled and the active substance specification has been suitably justified.

The active substance specification is considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided.

All excipients with the exception of red ferric oxide are the subjects of monographs in the European Pharmacopoeia. Compliance with the requirements of the pharmacopoeia is therefore applied as the specification for each of these substances. Red ferric oxide complies with the requirements of the United States Pharmacopoeia/National Formulary.

D. Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

There are no substances within the scope of the TSE Guideline present or used in the manufacture of these products.

E. Control on intermediate products

There are no intermediate products.

F. Control Tests on the Finished Product

The finished product specification controls the relevant parameters for the pharmaceutical form. The tests in the specification, and their limits, have been justified and are considered appropriate to adequately control the quality of the products.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification.

G. Stability

Stability data on the active substance have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions.

Stability data on the finished products have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life.

H. Genetically Modified Organisms

Not applicable

J. Other Information

Special precautions for storage:

Do not store above 25°C.

Store in the original container.

Keep the container tightly closed to protect from moisture.

Do not remove the desiccant.

Shelf life

Shelf-life of the veterinary medicinal product as packaged for sale:

Vidalta 10 mg prolonged-release tablets for cats: 18 months

Vidalta 15 mg prolonged-release tablets for cats: 24 months

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACOTOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

Pharmacodynamics

Carbimazole is an antithyroid drug of the mercaptoimidazole family of compounds. These antithyroid compounds reduce the thyroid glands' activity as a result of interfering with the thyroid hormone synthesis process by inhibiting thyroid peroxidase and by complexing molecular iodine.

Pharmacokinetics

Carbimazole is a carboxy derivative of methimazole, and is rapidly absorbed in the GI tract after oral administration, then quickly and fully metabolised into methimazole. It is methimazole which then acts on the target sites and elicits the desired effects. Methimazole accumulates preferentially in the thyroid glands and also the adrenal glands, but is distributed throughout the body. The pharmacokinetics of this drug are similar in rats, cats and humans. Elimination occurs mostly via the urine in the rat, although not so much in humans, where renal insufficiency doesn't seem to have much effect on the rate of elimination, but hepatic failure induces an impairment-proportional elongation of elimination time.

Toxicological Studies

Single Dose Toxicity

The applicant has provided bibliographical data for studies conducted intraperitoneally, orally and subcutaneously in mice, orally and subcutaneously in rats and orally in humans. Subcutaneous LD₅₀³ value in rats was 1050 mg/kg, and in mice was 345 mg/kg. Oral LD₅₀ value in rats was 2250 mg/kg, and in mice was 860 mg/kg. In humans, oral dose of 492 mg/kg over 88 weeks caused changes in gonadotropins and agranulocytosis; oral dose of 13 mg/kg over 33 days caused ear tumours, excitement and GI changes. Another study into the olfactory damage caused by methimazole in rats showed that a single oral dose of 50 mg/kg caused olfactory mucosal damage.

Repeated Dose Toxicity

Reference was made to a study where rats were administered a diet with the equivalent of 9 mg/kg bodyweight daily for up to 6 months. There were no physical signs of toxicity, except for an effect on bodyweight. Thyroid weight increased with duration of exposure, and effects seen on post-mortem included hypertrophy and hyperplasia of follicular cells, decreased colloid and increased vascularity. This study showed that the thyroids returned to their normal size on withdrawal of the drug, but still had larger than normal follicles.

³ LD₅₀ is the dose that kills half (50%) of the animals tested.

Reproductive Toxicity, including Teratogenicity:

The applicant made reference to a study where methimazole was administered to female rats at a dietary level of 0.1% for 14 - 22 days. There was a slight effect on the average number of young and weight per litter if administered during the preconception period. There were signs of increased gestation time and inactivity in those administered methimazole prior to conception and during gestation.

In another reference methimazole was fed to newborn male rats from day 1 to day 60 postpartum, via the mothers' milk or drinking water. There were effects such as reduced seminiferous tubule and lumen diameter. The proliferation and differentiation of germ cells were arrested and their numbers were decreased. Plasma testosterone, oestradiol and sex hormone binding globulin levels were significantly decreased and ventral, dorsolateral prostate and epididymis weights were decreased after 30 days+ administration.

Embryotoxicity/foetotoxicity (inc. teratogenicity)

The applicant has provided bibliographic data. A few cases of scalp defects, choanal atresia, intestinal abnormalities and cardiovascular defects have been described in newborn (human) infants whose mothers had taken methimazole during pregnancy at normal human dose levels. The first trimester of pregnancy seems to be the most sensitive for these effects.

Continuous administration of methimazole via drinking water (0.1 mg/ml) from day 16 of pregnancy to day 10 postpartum produced developmental delays in mice offspring.

Methimazole has not been shown to have teratogenic activity in rabbits, but has been shown to cause abnormal development in rat embryos at high doses.

Mutagenicity

The applicant has provided bibliographic data. Methimazole has been shown to induce severe chromosome aberrations in cultured mammalian cells; chromatid gaps, isochromatid gaps, breaks and exchanges were significantly increased.

Methimazole has been shown in mice not to induce chromosomal aberrations in spermatogonium, spermatocyte or bone marrow cells at levels up to 180 mg/kg, nor did it increase the number of micronuclei in bone marrow cells. However, it increased the number of cells with a large micronucleus.

Methimazole has been shown to decrease mitotic activity in peripheral blood culture. This effect was dose related tested at levels of 2.5 µg/ml and 5 µg/ml.

Another study submitted showed that methimazole interfered with the normal proliferation of T-lymphocytes by suppressing the production of T-cell growth factor, as well as inducing a higher incidence of sister-chromatid exchange during cell division.

In a dominant lethal mutation assay, it was shown to be negative.

Carcinogenicity

A number of references were provided to which the overall conclusion is that there is inadequate evidence to show that this is a carcinogen in humans.

Other Studies

Methimazole has been found to affect many different parts of the body in different ways, including inhibition of dopamine β -hydroxylase in rats, impairment of the immune system in mice, as well as having an anti-inflammatory effect greater even than aspirin. Some studies showed that methimazole causes olfactory mucosal damage at doses of ≥ 25 mg/kg ip in rats (NOAEL⁴ = 2 mg/kg ip) and at doses of 50 mg/kg orally (NOAEL = 25 mg/kg po).

Observations in Humans

Both carbimazole and methimazole have been extensively used in human patients for the same indications as are intended for this product and a number of references have been provided.

There have been many adverse reactions reported in humans, with a 3-5% prevalence; the most common being dermatological problems as well as nausea, arthralgia and cutaneous vasculitis. Some less common, but more serious reactions include bone marrow abnormalities and pure red cell anaemia. These substances have been shown to exacerbate cholestatic jaundice/hepatitis as part of an immune-mediated reaction and induce earache and loss of high-frequency hearing due to hypersensitivity reactions.

User Safety

The applicant has provided a satisfactory user risk assessment, identifying the users of the products and the potential routes of exposure for the operator. The following warnings are included on the SPC and product literature:

- Wash hands with soap and water after use and when handling litter used by treated animals.
- Do not handle this product if you are allergic to antithyroid products. If allergic symptoms develop, such as a skin rash, swelling of the face, lips or eyes or difficulty in breathing, you should seek medical attention immediately and show the package leaflet or label to the doctor.
- As carbimazole is a suspected human teratogen, women of child-bearing age should wear gloves when handling litter or vomit of treated cats.
- Pregnant women should wear gloves when handling the product.
- Do not break or crush tablets.

⁴ NOAEL - No observed adverse effect level

- Do not eat, drink or smoke while handling the tablet or used litter.
- In the case of accidental ingestion, seek medical advice immediately and show the package insert or the label to the physician.
- Carbimazole, as a prodrug of thiamazole (methimazole), may cause vomiting, epigastric distress, headache, fever, arthralgia, pruritus and pancytopenia. Treatment is symptomatic.

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required. Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the products are used as directed.

IV CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

Pharmacodynamics

The large amount of scientific information on the pharmacological aspects of mercaptoimidazoles in rodents and other mammals (including the target species) is adequate to justify the absence of further pharmacodynamic studies using these products.

Pharmacokinetics

The applicant conducted several pharmacokinetic studies in cats. These studies demonstrated the prolonged release properties of the formulation when compared to a conventional human preparation, Neo-mercazole. These tablets were slightly less bioavailable than Neo-mercazole but its absolute bioavailability was still high. Bioavailability is moderately improved by administration of the tablets with food and there was no evidence of accumulation of the prolonged release formulation after repeated daily dosing. The applicant presented a further *in-vivo* bioequivalence study which showed that Vidalta 10 mg prolonged-release tablets for cats and Vidalta 15 mg prolonged-release tablets for cats had the same relative bioavailability with the confidence intervals for the ratios of C_{max} ⁵ an AUC⁶ falling within the acceptable wider limits of 70%-143%.

Tolerance in the Target Species of Animals

Adverse reactions to carbimazole/methimazole are common and well documented in the literature where the incidence rate is reported as approximately 18%. Anorexia and vomiting are the most frequent signs, developing within the first month of treatment and usually resolving despite continued treatment. Facial excoriations have also been reported. Less common SARs⁷, such as hepatopathy, severe leucopenia and thrombocytopenia are more serious and require cessation of treatment. There is a suggestion in laboratory species that mercaptoimidazoles may cause immunomodulation and this may be involved with the SARs reported. A deterioration of pre-existent renal dysfunction, as a consequence of reduced GFR subsequent to correction of hyperthyroidism, is also noted. From reports in literature references, it appears that adverse reactions are reversible on withdrawal of medication. Appropriate warnings have been added to the SPC;

⁵ Maximum concentration

⁶ Area under the curve

⁷ SARs - Suspected adverse reactions

product use and dose should be according to the benefit/risk assessment for the individual case.

The first study was conducted to analyse the use of Vidalta 15 mg tablets administered orally once daily at 1x, 3x or 5x the recommended dose for 90 days. The study was conducted in accordance with GLP. A suitable number of cats were divided into different groups. A placebo group was also included. The animals were monitored and any adverse reactions analysed. The study showed that these tablets were well tolerated by healthy cats when administered at the recommended starting dose of 15 mg daily. However, this study did not enable determination of a therapeutic margin to confirm the safety of dose higher than 15 mg used to control hyperthyroidism in the clinical trial. This risk is mitigated by the warning in section 4.5.i. of the SPC: "doses above 20 mg have only been trialled in a small number of cats. Therefore, careful monitoring is recommended and the dose should be adjusted according to the benefit/risk assessment for the individual case."

The second study was conducted to analyse the use of Vidalta tablets at 1x, 3x and 5x the proposed clinical dose of one 15 mg tablet, over a period of six months. A suitable number of cats were divided into different group and a placebo group was included. The animals were monitored and any adverse reactions analysed. The findings of this study led to the inclusion of an additional warning in section 4.6 and 4.10 of the SPC regarding the potential for GI haemorrhage.

IV.B Clinical Studies

The applicant conducted two field studies to confirm the efficacy of product in cats with hyperthyroidism.

Field Trials

Study 1

Study title	A field trial to confirm the efficacy of controlled-release Vidalta tablets in cats with hyperthyroidism
Objectives	To confirm the efficacy and safety of prolonged-release Vidalta tablets in client-owned cats with newly diagnosed hyperthyroidism
Test site(s)	Multi-centre field trial
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	Vidalta 10 mg containing 10 mg carbimazole per tablet Vidalta 15 mg containing 15 mg carbimazole per tablet Initially one tablet of Vidalta 15 mg was given once daily
Animals	40 cats with clinical signs of hyperthyroidism Inclusion criterion: <ul style="list-style-type: none"> Basal serum TT4 concentration of ≥ 50 nmol/l Exclusion criteria <ul style="list-style-type: none"> Treatment with any anti-thyroid agent in the 4 weeks preceding the pre-inclusion visit Treatment with any medication which could interfere with the evaluation of treatment, including, corticosteroids, progestagens, immunosuppressive drugs in the 4 weeks before the pre-inclusion visit Coexisting primary disease that may affect the response to CBZ, including: major organ failure, severe cardiac dysfunction or chronic renal insufficiency Rectal temperature $> 40^{\circ}\text{C}$ Pregnancy or lactation
Randomisation	None
Blinding	None
Method	Veterinary examinations were conducted at pre-inclusion and at each subsequent visit. Owners

	<p>reported any adverse events to the veterinarian</p> <p>At each visit, owners documented overall attitude/behaviour, appetite and water intake of the cat compared to the previous visit. The Investigator recorded his/her clinical assessment of the stabilisation of the cat over the elapsed period. Cats were classified as hypothyroid, euthyroid or hyperthyroid, based on the evolution of clinical signs and on the TT4 concentration.</p>
Statistical method	<p>The level of significance was set at $\alpha=0.05$, with p-values between 0.05 – 0.10 indicating a trend.</p> <p>TT4 concentration, body weight and heart rate were analysed with repeated measures ANOVA using a linear mixed model with time of treatment as fixed effects. If statistical significance was reached, values at each regular visit were compared with the pre-inclusion value using an appropriate comparison test.</p> <p>The evolution of other parameters was only reported as descriptive statistics.</p>
RESULTS	
Outcomes for endpoints	<p>The response rate based on the TT4 was 75% at the end of the dose adjustment phase and 67% at the end of the maintenance phase. However, in terms of clinical assessment, 78% and 96% were euthyroid at the end of the dose adjustment and maintenance phases respectively.</p> <p>There was a significant reduction in TT4 compared to pre-inclusion levels as early as 10 days after treatment initiation. The median decrease in TT4 was 73% at the end of the dose adjustment period, and values remained stable up to 12 months. The rate of responders was based on the primary efficacy criterion of TT4 < 50 nmol/l. However, based on TT4 and clinical assessment, a significant response to treatment was seen in the non-responders with all cases showing a decrease in TT4 over the dose adjustment period (median decrease 56%).</p> <p>At the end of the maintenance phase, all non-responders (except 1 case) showed a decrease of TT4 (median 69%), and all except one case was clinically assessed as euthyroid.</p> <p>Poor response to treatment, or relapse was in most cases due to inadequate dose adjustment or emergence of concomitant disease.</p>
DISCUSSION	<p>This study confirmed the efficacy of controlled-release Vidalta tablets in cats with hyperthyroidism</p>

Study 2

Study title	A multi-centre and self-controlled clinical trial to confirm the efficacy and safety of Vidalta extended-release tablets in cats with hyperthyroidism and hyperthyroidism-associated clinical signs
Objectives	Evaluation and confirmation of the dose regimen, effectiveness and safety of Vidalta extended-release tablets for the treatment of hyperthyroidism and hyperthyroidism associated clinical signs in cats not previously treated with anti-thyroid agents
Test site(s)	Multi-centre field trial
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	Vidalta 10 mg containing 10 mg carbimazole per tablet Vidalta 15 mg containing 15 mg carbimazole per tablet Initially one tablet of Vidalta 15 mg was given once daily
Animals	Cats of any age, sex, breed and bodyweight; 161 cats were enrolled onto the study Inclusion criterion: <ul style="list-style-type: none"> • Total basal serum thyroxin (TT4) >5.0 µg/dl • Complete blood count (CBC) and chemistry panel within acceptable range (at the discretion of the investigator) • Negative serum antibody titres. • Demonstration of at least one of the following clinical signs: hyperactivity, weight loss, polyphagia, vomiting, diarrhoea, polyuria, polydipsia, tachycardia, arrhythmia Exclusion criteria <ul style="list-style-type: none"> • Presentation with clinical signs, serum biochemistry or haematology results indicating a severe concurrent disease that might have affected the response to carbimazole treatment • Rectal temperature > 104.0 °F • Confirmed pregnancy or lactation • Diagnosed diabetes mellitus • Administration of any anti-thyroid agent prior to pre-enrolment • Receiving phenobarbital treatment
Randomisation	None

Blinding	None
Method	<p>Full physical exam including body weight prior to start of study and at all subsequent visits.</p> <p>The cats were assessed for hyperactivity, weight, polyphagia, vomiting, diarrhoea, polyuria, polydipsia, tachycardia and arrhythmia on specific days. The overall clinical sign assessment was carried out on day 21. The evaluation of haematological parameters (haematocrit, mean corpuscular volume (MCV), mean corpuscular haemoglobin concentration (MCHC), haemoglobin, platelet count, white cell count, white cell differential) was conducted on specific days.</p> <p>Evaluation of the following parameters was also conducted on specific days (pre-enrolment visit only), amylase, lipase, AST, GGT, ALT, ALKP, bilirubin, creatinine, urea, glucose, sodium, chloride, potassium, phosphorus, calcium, total protein, albumin, globulin, CPK.</p>
Statistical method	<p>The null hypothesis was tested against the proposed hypothesis, using a one-sided significance level of $\alpha=0.05$. Two sided 90% confidence intervals for the proportion of responders were reported.</p> <p>Descriptive statistics, profile plots, and repeated measures analysis were performed on the data on secondary variables and safety monitoring criteria, as appropriate.</p>
RESULTS	
Outcomes for endpoints	<p>For the primary effectiveness variable, 68.12% of cats fulfilled the criteria for reduction in TT4 levels and clinical signs associated with hyperthyroidism at day 21 compared with at the enrolment examination. This was significantly greater ($p<0.0001$) than the 50% threshold stipulated in the study protocol.</p> <p>Over the course of the study, mean TT4 levels gradually rose from the day 21 result; the applicant postulates that this may be due to a reduction in client compliance over time. This was plausible, and it was also noted that the population of cats did not remain constant due to withdrawal and mortality of cats as the study progressed.</p> <p>Secondary variables such as body weight, heart rate and respiratory rate demonstrated response to treatment of as study cats gained weight, and showed reductions in heart and respiratory rate; these changes were maintained during the study. Body temperature also showed a small reduction, but all mean values were within the normal range.</p>

DISCUSSION	This study confirmed the efficacy and safety of Vidalta tablets in cats with hyperthyroidism and hyperthyroidism-associated clinical signs
------------	--

V OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics, the benefit/risk profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

MODULE 4

POST-AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the Heads of Medicines Agencies (veterinary) (HMA(v)) website (www.hma.eu).

This section contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.

POST-AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the Product Information Database of the Veterinary Medicines Directorate website.

www.gov.uk/check-animal-medicine-licensed

The post-authorisation assessment (PAA) contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.

The PAA for this product is available on the Product Information Database of the Veterinary Medicines Directorate website.

www.gov.uk/check-animal-medicine-licensed