PRODUCT MONOGRAPH

ACID CONTROL
(famotidine) USP
10 mg tablets

Histamine H_2 Receptor Antagonist

Vita Health Products Inc.
150 Beghin Avenue
Winnipeg, MB
Canada R2J 3W2

Date of Preparation:
January 6, 2016

Control Number: 190046

PRODUCT MONOGRAPH

ACID CONTROL
(famotidine) USP
10 mg tablets

THERAPEUTIC CLASSIFICATION

Histamine H_2 Receptor Antagonist

ACTION AND CLINICAL PHARMACOLOGY

Famotidine is a competitive inhibitor of histamine H_2-receptors. Inhibition of gastric juice secretion is its primary clinically important pharmacologic activity. The acid and pepsin content, as well as the volume, of basal, nocturnal, and stimulated gastric secretion is reduced by famotidine.

A comparative, two-way single dose bioavailability study was performed on two famotidine 10 mg pink formulations, ACID CONTROL and PEPCID® AC. The pharmacokinetic data calculated for famotidine in the ACID CONTROL and PEPCID® AC tablet formulations are tabulated below:

	Geometric mean Arithmetic mean (CV		
	ACID CONTROL 1 x 10 mg Tablet	Pepcid® AC 1 x 10 mg Tablets	Ratio (%) Geometric Mean
AUC_T (ng•h/mL)	218.1 228.5 (30)	227.9 234.4 (24)	95.7
AUC_I (ng• h/mL)	226.1 236.2 (29)	234.6 241.1 (23)	96.4
Cmax (ng/mL)	36.0 37.5 (29)	37.8 39.4 (30)	95.2
Tmax* (h)	2.69 (1.3)	2.54 (1.0)	-
$T_{1/2}$* (h)	3.30 (1.0)	3.14 (0.81)	-
*For the Tmax and $T_{1/2}$ parameters these are the Arithmetic means (standard deviation). ** Pepcid® AC 10 mg Tablets (Merck Frosst Canada Inc., Canada).			

INDICATIONS AND CLINICAL USE

ACID CONTROL (famotidine) is indicated in the treatment of the following conditions where a controlled reduction of gastric secretion is required, such as acid indigestion, heartburn, sour or upset stomach. ACID CONTROL is also indicated for the prevention of these symptoms when associated with the consumption of food and/or beverage.

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

PRECAUTIONS

General:

In clinical trials, patients with other underlying acid gastrointestinal diseases (e.g. duodenal ulcer, gastric ulcer) did not experience complications; in general, they did not exhibit a clinically significant deterioration in their condition. However, if patients have difficulty swallowing or if abdominal discomfort persists, the underlying cause should be determined. Symptomatic response to therapy with ACID CONTROL (famotidine) does not preclude the presence of gastric malignancy.

Patients with severe kidney disease, previous history of ulcer disease complications, severe coexisting illness, those who are experiencing unintended weight loss in association with dyspeptic symptoms, and those who are middle-aged or older with new or recently changed dyspeptic symptoms should consult a physician before commencing therapy with ACID CONTROL.

Patients consuming non-steroidal anti-inflammatory drugs may have dyspepsia as a side effect of these medicines and should consult a physician or a pharmacist before taking ACID CONTROL.

Therapy should not exceed two weeks of continuous treatment without medical consultation.

Drug Interactions

Studies with famotidine in man, in animal models, and *in vitro* have shown no significant interference with the disposition of compounds metabolized by the hepatic microsomal enzymes, e.g., cytochrome P450 system. Compounds tested in man have included warfarin, theophylline, phenytoin, diazepam, aminopyrine and antipyrine. Indocyanine green as an index of hepatic blood flow and/or hepatic drug extraction has been tested and no significant effects have been found.

Concomitant use of aluminum hydroxide/magnesium hydroxide at commonly used doses, does not influence the pharmacodynamics or bioavailability of ACID CONTROL. Famotidine does not affect gastric alcohol dehydrogenase and, consequently, blood ethanol levels.

Obstetrics:

Reproductive studies have been performed in rats and rabbits at oral doses of up to 2000 and 500 mg/kg/day, respectively (approximately 2500 and 625 times the maximum recommended prescription human dose [80 mg], respectively), and have revealed no evidence of impaired fertility or harm to the fetus due to famotidine. There are, however, no adequate or well-controlled studies in pregnant women.

Since the safe use of ACID CONTROL in pregnant women has not been established, pregnant women should not use ACID CONTROL unless directed otherwise by a physician.

Nursing Mothers:

Famotidine is detectable in human milk. Nursing mothers should either stop this drug or should stop nursing.

Pediatric Use:

Safety and effectiveness in children have not been established. ACID CONTROL should not be administered to children under12 years of age.

Use in Elderly Patients:

No dosage adjustment is required based on age (see HUMAN PHARMACOLOGY, Pharmacokinetics).

ADVERSE REACTIONS

ACID CONTROL (famotidine) has been demonstrated to be generally well tolerated. Adverse reactions reported in ≥ 1% of patients were headache and dizziness. These occurred with comparable frequency in patients treated with placebo.

Laboratory parameters may be affected during treatment with ACID CONTROL, but the changes are usually not considered serious. Among the laboratory changes that were reported during clinical trials were increases in AST, ALT, and WBC count, and decreases in hemoglobin and hematocrit. These changes were rarely of clinical significance.

No famotidine-treated patients/subjects had to be discontinued from therapy because of laboratory adverse experiences.

During marketed use of prescription doses, which are higher than those recommended for non-prescription use, the following adverse reactions have been reported; urticaria, liver enzymes abnormalities, cholestatic jaundice, anaphylaxis, angioedema. Toxic epidermal necrolysis has been reported very rarely with H_2-receptor antagonists.

The following adverse reactions have been reported; however, a causal relationship to therapy with ACID CONTROL has not been established: agitation, confusion, hallucinations, grand mal seizures, rare cases of impotence, thrombocytopenia, pancytopenia, leukopenia and granulocytosis.

Gynecomastia has been reported rarely. In most cases that were followed up, it was reversible after discontinuing treatment.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

To date, there is no experience with deliberate overdosage. No serious adverse effects have been observed when doses of up to 800 mg/day have been employed in patients with pathological hypersecretory conditions. Treatment should be symptomatic and supportive in the event of overdosage. Unabsorbed material should be removed from the gastrointestinal tract, the patient should be monitored, and supportive therapy should be employed.

The oral LD_{50} of famotidine in male and female rats and mice was >5000 mg/kg.

DOSAGE AND ADMINISTRATION

Adults and children 12 years of age or older: 10 mg, as required to relieve symptoms. For prevention of acid-related symptoms associated with the consumption of food and/or beverage: 10 mg one hour before eating. Repeat if symptoms return, up to a maximum of 20 mg in a 24-hour period.

Therapy should not exceed two weeks of continuous treatment without medical consultation.

Concomitant Use with Antacids:
Antacids may be given concomitantly if needed.

PHARMACEUTICAL INFORMATION

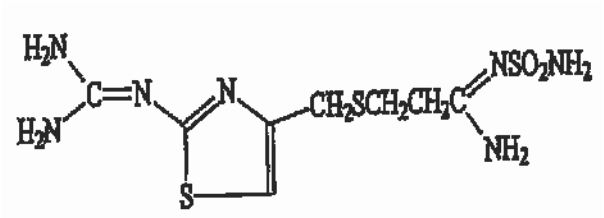
DRUG SUBSTANCE:

Trade Name: ACID CONTROL

Proper name: famotidine

Chemical name: N'-(aminosulfonyl)-3-[[[2-[(diaminomethylene)amino]-4-thiazolyl]methyl]thio]Propanimidamide.

Structural formula:



Molecular formula: $C_8H_{15}N_7O_2S_3$

Molecular weight: 337.44

Description: Famotidine is a white to pale yellow crystalline compound that is freely soluble in glacial acetic acid, slightly soluble in methanol, very slightly soluble in water and practically insoluble in ethanol.

Composition: Each tablet contains: carnauba wax, colloidal silicon dioxide, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, red iron oxide, starch, talc, titanium dioxide. In addition to the above ingredients, the brown tablets contain yellow iron oxide.

Stability and Storage Recommendations:

Bottles should be stored between 15° - 30° C and protected from light and high humidity. Unit dose strips should be stored between 15° - 25° C and protected from light and high humidity.

AVAILABILITY OF DOSAGE FORMS

ACID CONTROL (famotidine) is available as either:

10 mg: round, biconvex, pink coloured, film-coated tablets engraved 'FAM' and '10' on one side and plain on the other.

Supplied: 10 mg tablets are available in blister packs of 6, 12, 18, 30, 60 and 90.

INFORMATION FOR THE CONSUMER

WHAT IS ACID CONTROL?

ACID CONTROL (famotidine) Tablets are clinically proven to provide fast and effective relief from heartburn and acid indigestion. ACID CONTROL contains the ingredient famotidine which has previously been available only with a prescription. ACID CONTROL works by actually reducing the flow of excess stomach acid which can lead to heartburn pain, unlike antacids which neutralize existing stomach acid. One (1) ACID CONTROL tablet controls stomach acid for up to 9 hours. ACID CONTROL is available in small easy-to-follow film-coated tablets.

FOR WHAT CONDITIONS SHOULD IT BE TAKEN?

ACID CONTROL offers fast and effective relief from heartburn, acid indigestion and upset or sour stomach due to excess stomach acid. ACID CONTROL also prevents these symptoms brought on by consuming food and/or beverage.

HOW SHOULD ACID CONTROL BE TAKEN?

Adults and children 12 years of age or older: For relief of symptoms, take one (1) tablet. For prevention of acid-related symptoms brought on by consuming food and/or beverage, take one (1) tablet one hour before eating. If symptoms return, you may take another tablet. Do not take more than two tablets during a 24-hour period. If symptoms persist for more than two consecutive weeks, consult your physician.

WHEN SHOULD A PHYSICIAN OR PHARMACIST BE CONSULTED?

This medicine may not be suitable for some people. Consult with your physician or pharmacist before using if:

- You are allergic to any component of this product.
- You are pregnant or breast-feeding.

- You have difficulty swallowing, or persistent abdominal discomfort.
- You have severe kidney disease or any other severe illnesses.
- You are over 40 and you are experiencing new or recently changed symptoms of acid indigestion or heartburn.
- You are taking nonsteroidal anti-inflammatory drugs [NSAIDs] (because these medicines may be causing your symptoms).
- You have a previous history of ulcer disease complications.
- You are experiencing unintended weight loss in association with your symptoms of acid indigestion or heartburn.

ACID CONTROL is generally well tolerated. Should any unusual symptoms occur, a physician should be consulted.

WHAT ELSE CAN BE DONE TO HELP AVOID SYMPTOMS?

- Do not lie down soon after eating.
- If you are overweight, lose weight.
- If you smoke, stop or cut down.
- Avoid or limit foods such as caffeine, chocolate, fatty foods and alcohol.
- Do not eat just before bedtime.

DESCRIPTION

Each round, biconvex, pink or brown coloured, film-coated tablets has ‘FAM’ and ‘10’ engraved on one side and is plain on the other.

INGREDIENTS

Active ingredient:
Each ACID CONTROL Tablet contains 10 mg of famotidine.

Non-medicinal Ingredients:
Film-coated Tablets contain the following non-medicinal ingredients: carnauba wax, colloidal silicon dioxide, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, red iron oxide, starch, titanium dioxide. In addition to the above ingredients, the brown tablets contain yellow iron oxide.

HOW SHOULD ACID CONTROL BE STORED?

Blister packs should be stored between 15°C and 25°C and protected from light and high humidity. It is advisable to keep blisters in carton until all tablets are used.

Keep this and all medicines out of the reach of children.

Consult your physician or pharmacist if you need further information

Product Monograph available on request to physicians and pharmacists.

PHARMACOLOGY

I. HUMAN PHARMACOLOGY

In both normal volunteers and hypersecretors, famotidine inhibited basal nocturnal and daytime gastric secretion, as well as secretion stimulated by a variety of stimuli, such as pentagastrin and food.

After oral administration, a dose-response relationship was clearly demonstrated from 0.5 and 10 mg famotidine in terms of raising gastric pH between and after meals. Famotidine doses of 2.5 to 10 mg were demonstrated to produce a statistically significant effect on gastric pH as compared to placebo. The onset of effect for the 5 and 10 mg doses was seen at approximately 1.5 hours post dose while that of the 2.5 mg dose was not seen until 2.5 hours post dose. The maximum effect, as measured by peak mean pH value, occurred at 3.5 hours. The activity of the 5 and 10 mg dose continues until approximately 9 hours post dose. Famotidine was well tolerated at these dose levels.

Fasting and postprandial serum gastrin levels may be slightly elevated during periods of drug antisecretory effect, and with chronic therapy an increase in gastric bacterial flora may occur. Gastric emptying and exocrine pancreatic function are not affected by famotidine.

Other Effects:
Systemic pharmacologic effects of famotidine in the CNS, cardiovascular, respiratory or endocrine systems have not been found to date. After intravenous bolus doses of 20 mg famotidine, serum prolactin levels do not rise and no antiandrogenic effects have been detected.

Pharmacokinetics:
Famotidine is incompletely absorbed. The bioavailability of oral doses is 40-45%. Bioavailability may be slightly increased by food; however, this effect is of no clinical significance. Bioavailability of famotidine at recommended doses is not affected by customary doses of antacids. Famotidine undergoes minimal first-pass metabolism. Peak plasma levels occur in 1-3 hours after oral doses. Plasma levels after multiple doses are similar to those after single doses. In plasma, famotidine is 15 to 20% protein bound. The elimination half-life of famotidine is 2.5 to 3.5 hours. Famotidine is eliminated by renal (65 to 70%) and metabolic (30 to 35%) routes. Renal clearance is 250 to 450 mL/min., indicating some tubular excretion.

Twenty-five to 30% of an oral dose and 65-70% of an intravenous dose are recovered in the urine as unchanged compound. The s-oxide is the only metabolite identified in man. There is a close relationship between creatinine clearance values and the elimination half-life of famotidine. Elimination half-life of famotidine may exceed 20 hours in patients with severe renal insufficiency, i.e., creatinine clearance less than 10 mL/min., and adjustment of dosing intervals may be necessary (see PRECAUTIONS, DOSAGE AND ADMINISTRATION). There are no

clinically significant age-related changes in the pharmacokinetics of famotidine in elderly patients.

II. ANIMAL PHARMACOLOGY

Gastric secretion evoked by histamine and other secretagogues is inhibited by famotidine. After oral or intravenous administration of famotidine to dogs, the ED_{50} was 0.03 mg/kg. Gastric secretion was inhibited for at least 24 hours in dogs after an oral dose of 2.1 mg/kg. An oral dose of 3 mg/kg one hour prior to feeding inhibited the acid response in dogs during a 4-hour post feeding period by an average of 96%.

Mechanism of Action:
Famotidine is a specific, competitive, H_2-receptor antagonist. There was no effect *in vitro* on responses mediated by H_1-histamine, beta, adrenergic, or cholinergic receptors. In radioligand binding to dopaminergic, neuroleptic, serotonergic, adrenergic, cholinergic, and purinergic sites famotidine was inactive. Famotidine was also inactive in an androgen receptor assay.

The interaction between famotidine and H_2-receptors is tissue-dependent. The effects of famotidine were surmountable and readily reversible on washout in guinea pig lungs and rabbit gastric glands, indicating classic competitive inhibition at the H_2-receptor sites. However, famotidine acted as a non-competitive H_2 antagonist in guinea pig atria, and recovery after washout of famotidine was retarded.

Absorption and Distribution:

Two animal species were used to study the absorption, distribution, metabolism and excretion of famotidine. Absorption was 28% in the rat and 43% in the dog. No tendency for the drug to accumulate was indicated as the plasma half-life in dogs, 2.5 hours, was unchanged after repeated doses. The highest levels of radioactivity after an oral dose of famotidine in rats were found in the gastrointestinal tract, kidneys, liver, submandibular glands, arteries, epiphyseal membrane, fascia, and uvea. The distribution pattern was not affected on repeated dosing. Famotidine did not effectively cross the blood-brain or placental barrier of rats. It was present in rat milk.

Metabolism and Excretion:
The sulfoxide derivative, which was present in minor amounts, was the only metabolite of famotidine in rat and dog urine. Urinary and fecal excretion of radioactivity in rats accounted for 28% and 70%, respectively, of an oral dose, compared to 83% and 17% respectively, of an intravenous dose. About 2.4% of the dose in rats was excreted in the bile. Forty-five percent of an oral dose in the urine of dogs, compared to 100% of an intravenous dose.

Effects on Liver Microsomal Drug-Metabolizing Enzymes:
Pentobarbital or hexobarbital sleeping times and it ascorbic acid excretion are not affected by famotidine, suggesting that famotidine does not induce drug-metabolizing enzymes. Famotidine caused none of the changes induced by cimetidine on the pharmacokinetics of diazepam, warfarin, and propranolol. Famotidine produced only minimal suppression of aminopyrine and

diazepam N-demethylase activity *in vitro*, and showed little affinity for testosterone hydroxylases of mouse liver *in vitro*.

Gastrointestinal Effects other than Antisecretory:
Gastric erosions induced in rats by cold restraint, water immersion, pyloric ligation, or drugs such as acetylsalicylic acid, histamine or prednisolone, were prevented by famotidine, as were duodenal ulcers caused by cysteamine and mepirizole. The healing of the gastric lesions induced by acetic acid and the duodenal ulcers produced by mepirizole was significantly accelerated by famotidine.

The antiulcer effect of famotidine plus magnesium and aluminum hydroxides was greater than the sum of the effects of these drugs used separately.

The gastric lesions and hemorrhage resulting from blood removal and histamine injection in anesthetized rats were inhibited by famotidine.

Famotidine had no effect on the concentration of gastric mucosal histamine in normal rats, but it did reduce the levels of cAMP, particularly in response to histamine stimulation.

Famotidine had no effect on the intragastric electropotential in anaesthetized cats, when tested at intragastric doses more than ten-fold greater than those required to block gastric secretion maximally.

Cardiorenal Effects:
The cardiorenal effects of famotidine were studied in dogs and rats. Oral administration of 10 mg/kg of famotidine to spontaneously hypertensive rats was without effect on the blood pressure. Intravenous administration of 1.0 and 4.0 mg/kg of famotidine to anaesthetized dogs was without effect on cardiovascular parameters relating to the autonomic nervous system, blood pressure, heart rate, or respiratory function. An oral dose of 10 mg/kg in conscious dogs was without diuretic effect.

Central Nervous System Effects:
The effects of famotidine on the central nervous system were studied in squirrel monkeys, mice, and cats. Famotidine had a bidirectional effect on lever pressing (avoidance response) in monkeys, causing an increase at the low dose (1.0 mg/kg p.o.) and a small decrease at 9 mg/kg. Following intraperitoneal administration of 6 to 150 mg/kg to mice, no overt behavioral signs or symptoms of central nervous system activity were observed. In mice, famotidine was not active as an antagonist of the CNS actions of TRH, neurotensin, substance P, or amphetamine. Famotidine was free of major or minor tranquilizing, anticonvulsant, anticholinergic, ganglionic blocking, or dopaminergic activity. Famotidine did not affect the EEG or arousal response in cats, but did prolong the duration of hippocampal after-discharge. Only 4% of the plasma concentration of the drug was detected in the cerebrospinal fluid.

TOXICOLOGY

Acute Toxicity:

Species	Sex	Route	LD_{50} (mg/kg)
Mouse	M F	P.O.* P.O.*	4,684 3,233
Mouse	M F	I.V. (4%) I.V. (4%)	254 358
Rat	M F	P.O.* P.O.*	4,907 4,049
Rat	M F	I.P I.P	987 814

* In solution (acidic, 50-55°C deionized water).

Subacute and Chronic Toxicity:

In subacute studies, famotidine is well tolerated by both rats and dogs at doses of 2 g/kg twice a day orally and at doses up to 1000 or 2000 mg/kg/day for one year in these species. In rats given 200 mg/kg/day or more of the compound, eosinophilic cytoplasmic granularity of gastric chief cells was seen at a higher incidence compared to controls. This is considered as a secondary effect due to the exaggerated pharmacologic activity of the compound and at these extremely high dosage levels and is considered of no toxicologic significance. In a 106-week study in rats designed to study the carcinogenic potential of the compound, this gastric change did not progress to hyperplasia or neoplasia. Similarly, no evidence of a neoplastic potential was shown in mice (given the compound for 92 weeks). Based on the results from studies performed using pharmacologically-related compounds, this change was fully reversible.

Famotidine was well tolerated by rats for 13 weeks at dosage levels of up to 20 mg/kg/day i.v. and by dogs, except for occasional emesis, at dosage levels of up to 10 mg/kg/day for 5 to 26 weeks.

Reproduction Studies:

Fertility and reproductive performance were not affected in studies with rats given oral doses of up to 2000 mg/kg/day or intravenous doses of up to 200 mg/kg/day (approximately 2500 and 250 times the maximum recommended prescription human dose, respectively),

No evidence of embryolethality or teratogenicity was revealed when famotidine was given orally to pregnant rats in doses of up to 2000 mg/kg/day or intravenously in doses of up to 200 mg/kg/day, from Days 7 to 17 of pregnancy.

Oral administration of famotidine to pregnant rabbits from Days 6 to 18 of pregnancy at dosage levels up to 500 mg/kg/day revealed no evidence of embryolethality or teratogenicity.

Mutagenicity:

No mutagenic potential was seen when famotidine was tested in a reverse-mutation test in a reverse-mutation test (Ames test) using *Salmonella typhimurium* and *Escherichia coli* with and

without metabolic activation. These same studies were performed with famotidine/sodium, nitrite reaction mixture and C-nitroso derivatives of famotidine and they were also negative. Famotidine and C-nitroso derivatives of famotidine were tested in the rec-assay using *Bacillus subtilis* H17 and M45 and the tests were negative for DNA-damaging capacity of the compounds. A micronucleus test and a chromosomal aberration test showed no evidence of a mutagenic effect in *in vivo* studies in mice.

Carcinogenicity:
No evidence of a carcinogenic potential was seen in a 92-week oral carcinogenicity study conducted in mice at doses of 20, 200 and 2000 mg/kg/day. A 106-week oral carcinogenicity study in rats given doses of 20, 200 and 2000 mg/kg/day did not reveal any carcinogenic potential for famotidine.

Special Studies:
After five weeks of oral administration at doses up to 2000 mg/kg/day, the effects of famotidine on the thyroid of rats were evaluated. No evidence of treatment-related alterations of serum thyroid hormone levels, thyroid weight or the microscopic appearance were seen after administration of famotidine.

In immunogenicity studies, no effect on the production of IgE antibodies was seen in the sera of mice which were injected, once intraperitoneally, with famotidine alone (up to 2 mg/8 mL/kg) or coupled with either mouse serum albumin or ovalbumin. The sera were used to measure passive cutaneous anaphylaxis in rats which were then challenged with solutions of antigens similar to those antigens used for the initial dose in mice. Similarly, no evidence of an anaphylactic reaction was seen in guinea pigs challenged intravenously with famotidine after initiating doses (three times, subcutaneously, at six-day intervals) of up to 10 mg/mL.

REFERENCES

1. Barzaghi N, Gratti G, Crema F, Perucca E. Impaired bioavailability of famotidine given concurrently with a potent antacid. J Clin Pharmacol 1989;29:670-72.

2. Echizen H, Ishizaki T. Clinical pharmacokinetics of famotidine. Clin Pharmacokin 1991;21:178-94.

3. Hayakawa A, Che K, Miyoshi A, Harasawa S, Miwa T, Makabatake T. Properties of famotidine in relation to safety. Ital J Gastroenterol 1984;16:174-176.

4. Lin JH, Chremos AN, Kanovsky SM, et al. Effects of antacids and food on absorption of famotidine. Br J Clin Pharmac 1987:24:551-53.

5. McCallum RW, Kuljian B, Chremos AN, Tupy-Visich MA, Huber PB. Prolonged gastric antisecretory effect of a novel H_2-receptor inhibitor, MK-208. Gastroenterology (in Soc. Proc.) 1983;84:1245.

6. Product Monograph for Pepcid AC 10 mg Tablets. Frosst – Division of Merck Frosst Canada Inc. Canada. February 5, 1996.

7. A comparative two-way, single-dose bioavailability study of famotidine 10 mg tablets in fasting volunteers. Completed October 1996. Data on file at Novopharm Limited.

8. Product Monograph for Acid Control (famotidine) USP 10 mg Tablets. Teva Canada Limited. Control number 172917. May 1, 2014.