EGATEN- triclabendazole tablet
Novartis Pharmaceuticals Corporation

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use EGATEN safely and effectively. See full prescribing information for EGATEN.
EGATEN® (triclabendazole) tablets, for oral use
Initial U.S. Approval: 2019

INDICATIONS AND USAGE

EGATEN® tablet is an anthelmintic indicated for the treatment of fascioliasis in patients 6 years of age and older. (1)

DOSAGE AND ADMINISTRATION

- The recommended dose of EGATEN is 2 doses of 10 mg/kg given 12 hours apart in patients 6 years of age and older. (2)
- Take orally with food. (2)
- Swallow tablets whole or divide in half and take with water, or crush and administer with applesauce. (2)
- If the dosage cannot be adjusted exactly, round dose upwards. (2)

DOSAGE FORMS AND STRENGTHS

Tablets: 250 mg, functionally scored. (3)

CONTRAINDICATIONS

Patients with known hypersensitivity to triclabendazole, other benzimidazole derivatives or any of the excipients in EGATEN. (4)

WARNINGS AND PRECAUTIONS

QT Prolongation: May prolong QT interval. Monitor ECG in patients with a history of QT prolongation or who are taking medications which prolong the QT interval. (5.1)

ADVERSE REACTIONS

Most common adverse reactions (greater than 2%) with triclabendazole 20 mg/kg dose are abdominal pain, hyperhidrosis, nausea, decreased appetite, headache, urticaria, diarrhea, vomiting, musculoskeletal chest pain, and pruritus. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

CYP2C19 Substrates: Re-check the plasma concentration of concomitantly administered CYP2C19 substrates after cessation of EGATEN therapy, if the plasma concentrations of the CYP2C19 substrates are elevated during administration of EGATEN. (7.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 9/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

EGATEN® is indicated for the treatment of fascioliasis in patients 6 years of age and older.

2 DOSAGE AND ADMINISTRATION

The recommended dose of EGATEN is 2 doses of 10 mg/kg given 12 hours apart in patients 6 years of age and older. The 250 mg tablets are functionally scored and divisible into two equal halves of 125 mg. If the dosage cannot be adjusted exactly, round the dose upwards.

Take EGATEN orally with food. EGATEN tablets can be swallowed whole or divided in half and taken with water or crushed and administered with applesauce. The crushed tablet mixed with applesauce is stable for up to 4 hours.

3 DOSAGE FORMS AND STRENGTHS

EGATEN (triclabendazole) tablet: 250 mg pale red, speckled, capsule shaped, biconvex with imprint of “EG EG” on one side and functionally scored on both sides.

4 CONTRAINDICATIONS

EGATEN is contraindicated in patients with known hypersensitivity to triclabendazole and/or to other benzimidazole derivatives or to any of the excipients in EGATEN.

5 WARNINGS AND PRECAUTIONS

5.1 QT Prolongation

Transient prolongation of the mean QTc interval was noted on the electrocardiographic recordings in dogs *[see Nonclinical Toxicology (13.2)]*. Monitor ECG in patients with a history of prolongation of the QTc interval or a history of symptoms compatible with a long QT interval or when EGATEN is used in patients who receive drugs that prolong the QT interval.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety of triclabendazole was evaluated in 208 adult and pediatric patients 5 years of age and older who participated in 6 clinical trials for the treatment of fascioliasis and received 10 mg/kg or 20 mg/kg of triclabendazole; of these, 6 patients failed the 10 mg/kg dose and were retreated with 20 mg/kg. The 10 mg/kg dosing regimen is not approved *[see Dosage and Administration (2)]*. In these trials, 186 patients received a single dose of 10 mg/kg and 28 patients received a dose of 20 mg/kg as two divided doses. Pooled data for adverse reactions reported in more than 2% of the patients in these clinical trials for the 10 mg/kg and 20 mg/kg dosing regimens are presented in Table 1.

Table 1: Adverse Reactions Occurring in >2% of Patients Who Received a Total of 10 mg/kg or 20 mg/kg Triclabendazole for Fascioliasis Treatment (Pooled across 6 studies)

Adverse Reactions	Triclabendazole 10 mg/kg N = 186, n (%)	Triclabendazole 20 mg/kg in two divided doses[1] N = 28, n (%)
Abdominal pain[2]	105 (56)	26 (93)
Hyperhidrosis	42 (23)	7 (25)
Vertigo	16 (9)	0
Nausea	15 (8)	5 (18)
Urticaria	12 (7)	3 (11)
Vomiting	11 (6)	2 (7)
Headache	11 (6)	4 (14)
Dyspnea	9 (5)	0
Pruritus	8 (4)	1 (4)
Asthenia	7 (4)	0
Musculoskeletal chest pain	7 (4)	1 (4)
Cough	7 (4)	0
Decreased appetite	6 (3)	5 (18)
Chest pain	6 (3)	0
Pyrexia	4 (2)	0
Jaundice[3]	4 (2)	0
Chest discomfort	4 (2)	0
Diarrhea	0	2 (7)

[1]Divided doses were given 6-48 hours apart
[2]Abdominal pain upper and abdominal pain
[3]Jaundice and ocular icterus

Adverse reactions reported in less than or equal to 2% of patients who received a total of 10 mg/kg of

triclabendazole were constipation, biliary colic, arthralgia, back pain, spinal pain, and chromaturia. Some adverse reactions associated with triclabendazole treatment in fascioliasis, e.g. abdominal pain, biliary colic, and jaundice, could be secondary to the infection and may be more frequent and/or severe in patients with a heavy worm burden.

The safety profile of triclabendazole 20 mg/kg in divided doses in a non-hepatic parasitic infection (N = 104) was generally similar to the safety profile in fascioliasis, except for a lower incidence of post-treatment abdominal pain.

Liver Enzyme Elevations

In clinical studies, up to one third of patients had liver enzyme elevations at baseline, which generally improved post-treatment. Of those with normal liver enzyme values at baseline, 6.8%, 4.5%, 4.2% and 3% of patients had post-treatment elevations in bilirubin, aspartate aminotransferase (AST), alkaline phosphatase (ALP) and alanine aminotransferase (ALT), respectively. Transient increases in liver enzymes and total bilirubin in fascioliasis patients receiving triclabendazole are reported in the literature.

6.2 Postmarketing Experience

Resistance to triclabendazole has been reported outside the United States *[see Microbiology (12.4)]*.

7 DRUG INTERACTIONS

7.1 Effect of EGATEN on CYP2C19 Substrates

No specific clinical drug interaction studies have been conducted for triclabendazole. However, in vitro data suggest the potential for increased plasma concentrations of CYP2C19 substrates with concomitant use of triclabendazole *[see Clinical Pharmacology (12.3)]*. The potential elevation in concentrations of concomitantly used CYP2C19 substrates is expected to be transient based on the short elimination half-life and short treatment duration of triclabendazole.

For those CYP2C19 substrate drugs that require therapeutic monitoring of systemic drug exposures, if the plasma concentrations of the CYP2C19 substrates are elevated during administration of triclabendazole, re-check the plasma concentration of the CYP2C19 substrates after cessation of triclabendazole therapy.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on EGATEN use in pregnant women to inform a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Reproductive studies in animals (rat and rabbits) have not shown a risk of increased fetal abnormalities with exposure to triclabendazole during organogenesis at doses approximately 0.3 to 1.6 times the maximum recommended human dose (MRHD) of 20 mg/kg based on body surface area comparison *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively.

Data

Animal Data

Embryo-fetal developmental toxicity studies revealed no malformations in rats and rabbits at doses up to

200 mg/kg/day and 20 mg/kg/day, respectively (approximately 1.6 times and 0.3 times the MRHD based on body surface area comparison, respectively). The animals were treated orally during organogenesis, starting on Day 6 of the pregnancy until Day 15 in rats and Day 18 in rabbits. Maternal toxicity was noted at doses greater than or equal to 100 mg/kg/day in rats and 10 mg/kg/day in rabbits, which was associated with lower fetus weights and delayed ossification. These findings were considered indicative of delayed physiological growth that was secondary to maternal toxicity. No increase in malformation or other abnormalities was observed at any dose level in either species.

8.2 Lactation

Risk Summary

There are no data on the presence of triclabendazole in human milk, the effects on the breastfed infant, or the effects on milk production. Published animal data indicate that triclabendazole is detected in goat milk when administered as a single dose to one lactating animal. When a drug is present in animal milk, it is likely that the drug will be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EGATEN and any potential adverse effects on the breastfed infant from EGATEN or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness of EGATEN has been established in pediatric patients aged 6 years and older.

Safety and effectiveness of EGATEN in pediatric patients below the age of 6 years have not been established.

8.5 Geriatric Use

Clinical studies of EGATEN did not include sufficient numbers of patients aged 65 and over to determine whether the elderly respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Renal Impairment

EGATEN has not been studied in patients with renal impairment.

8.7 Hepatic Impairment

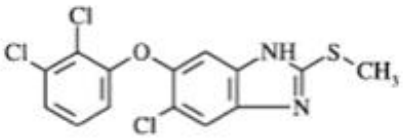
EGATEN has not been studied in patients with hepatic impairment.

10 OVERDOSAGE

The reported symptom of overdosage following ingestion of approximately 54 mg/kg of EGATEN (approximately 2.7 times the recommended dose) was nausea. The patient recovered following osmotic diuresis.

11 DESCRIPTION

EGATEN (triclabendazole) tablet is an orally administered anthelmintic for immediate release. Triclabendazole is designated chemically as benzimidazole derivative, 6-chloro-5-(2, 3-dichlorophenoxy)-2-(methylthio)-1H-benzimidazole (triclabendazole). The molecular formula for triclabendazole is $C_{14}H_9Cl_3N_2OS$ and the molecular weight is 359.65 g/mol. The chemical structure of triclabendazole is shown below:



Triclabendazole is a white or almost white, crystalline powder.

EGATEN tablets are pale red, speckled, capsule shaped, biconvex tablets, with imprint “EG EG” on one side and functionally scored on both sides. Each tablet contains 250 mg of triclabendazole.

Inactive Ingredients: colloidal silicon dioxide, iron oxide red, lactose monohydrate, maize starch, magnesium stearate, methylhydroxyethylcellulose.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Triclabendazole is an anthelmintic against *Fasciola* species *[see Microbiology (12.4)]*.

12.2 Pharmacodynamics

Triclabendazole exposure-response relationships and the time course of pharmacodynamics response are unknown.

12.3 Pharmacokinetics

After oral administration of a single dose of 10 mg/kg triclabendazole with a 560-kcal meal to patients with fascioliasis, mean peak plasma concentrations (C_{max}) for triclabendazole, the sulfoxide and sulfone metabolites were 1.16, 38.6, and 2.29 µmol/L, respectively. The area under the curve (AUC) for triclabendazole, the sulfoxide and sulfone metabolites were 5.72, 386, and 30.5 µmol·h/L, respectively.

Absorption

Following oral administration of a single dose of triclabendazole at 10 mg/kg with a 560-kcal meal to patients with fascioliasis, the median T_{max} for the parent compound and the sulfoxide metabolite was 3 to 4 hours.

Effect of Food

C_{max} and AUC of triclabendazole and sulfoxide metabolite increased approximately 3-fold and 2-fold respectively when triclabendazole was administered as a single dose at 10 mg/kg with a meal containing a total of approximately 560 kcal (consisting of 2 cups of sweetened white coffee, a roll with cheese, and a roll with butter and jam). In addition, the sulfoxide metabolite T_{max} increased from 2 hours in the fasted state to 4 hours in the fed state.

Distribution

The apparent volume of distribution (V_d) of the sulfoxide metabolite in fed patients is approximately 1 L/kg.

Protein-binding of triclabendazole, sulfoxide metabolite and sulfone metabolite in human plasma was 96.7%, 98.4% and 98.8% respectively.

Elimination

The plasma elimination half-life ($t_{1/2}$) of triclabendazole, the sulfoxide and sulfone metabolites in humans is approximately 8, 14, and 11 hours, respectively.

Metabolism

Based on in vitro studies, triclabendazole is primarily metabolized by CYP1A2 (approximately 64%)

into its active sulfoxide metabolite and to a lesser extent by CYP2C9, CYP2C19, CYP2D6, CYP3A, and FMO. This sulfoxide metabolite is further metabolized primarily by CYP2C9 to the active sulfone metabolite and to a lesser extent by CYP1A1, CYP1A2, CYP1B1, CYP2C19, CYP2D6 and CYP3A4, in vitro.

Excretion

No excretion data is available in humans. However, in animals, the drug is largely excreted via the biliary tract in the feces (90%), together with the sulfoxide and sulfone metabolite. Less than 10% of an oral dose is excreted in the urine.

Specific Populations

The pharmacokinetics of EGATEN were not studied in patients with renal or hepatic impairment.

Pediatric Patients

No dedicated pediatric pharmacokinetic studies were conducted. However, in one pharmacokinetic study of 20 patients, 7 children (ages 9 to 15 years) were dosed with triclabendazole 10 mg/kg single dose. AUC values of triclabendazole sulfoxide were 20% lower in these pediatric patients in the fed state than in the 13 patients above 15 years of age, but the difference was not statistically significant.

Drug Interaction Studies:

Clinical drug interaction studies have not been conducted for triclabendazole.

In Vitro Studies

Triclabendazole and its sulfoxide and sulfone metabolites have the potential to inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A at clinically relevant plasma concentrations, with the highest potential of inhibition on CYP2C19. No in vitro studies were conducted to assess the ability of triclabendazole and its metabolites to induce CYP enzymes. No in vitro studies were conducted to assess the ability of triclabendazole and its metabolites to induce or inhibit transporters.

12.4 Microbiology

Mechanism of Action

The mechanism by which triclabendazole exhibits its effect against *Fasciola* species is not fully elucidated. Studies in vitro and/or in infected animals suggest that triclabendazole and its active metabolites (sulfoxide and sulfone) are absorbed by the tegument of the immature and mature worms, leading to a decrease of the resting membrane potential, inhibition of tubulin function as well as protein and enzyme synthesis. These metabolic disturbances are associated with inhibition of motility, disruption of the surface as well as ultrastructure that includes inhibition of spermatogenesis and vitelline cells.

Antimicrobial Activity

Triclabendazole and its metabolites are active against the immature and mature worms of *Fasciola hepatica* and *Fasciola gigantica [see Clinical Studies (14)]*.

Resistance

Studies in vitro and in vivo as well as case reports suggest a potential for development of resistance to triclabendazole.

The mechanism of resistance may be multifactorial that include changes in drug uptake/efflux mechanisms, the target molecules, and altered drug metabolism. The clinical significance of triclabendazole resistance in humans is not established.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Mutagenesis

No genotoxic potential was noted for triclabendazole tested in a battery of 6 genotoxicity in vitro and in vivo assays which include a bacterial reverse mutation assay, chromosome aberration assays, and a micronucleus assay.

Impairment of Fertility

No drug-related effects on reproductive performance, mating ratios or fertility indices have been noted in a 2-generation reproductive and developmental toxicity study in rats. The animals were treated with up to 75 ppm triclabendazole via diet, amounting to a mean daily intake of 7.3 mg/kg/day (approximately 0.1 times the MRHD based on body surface area comparison) for a period of 110 days, which included a 12-day mating period beginning on Day 62 of dosing and continuing until the offspring were weaned.

13.2 Animal Toxicology and/or Pharmacology

Dietary administration of triclabendazole at a dose of 39 mg/kg/day (1.1-times the MRHD based on body surface area comparison) was associated with a transient increase in the QT and QTc intervals on weeks 5 and 9 in some dogs in a 13-week study resulting in QT (QTc) intervals of 212-227 (318-338) msec in the 39 mg/kg dose group (adjusted) compared to 190-193 (280-297) msec in controls. At Week 13, no statistically significant differences were noted between the treatment and control groups.

Additionally, when dogs were administered triclabendazole at a single dose of 40 or 100 mg/kg (1.1 or 2.7 times the MRHD based on body surface area comparison), increase in QTc intervals was observed resulting in QTc intervals of 217-247 msec compared to a normal (historical control) of 193-231 msec. However, plasma levels of the sulfone metabolite in dogs (which is thought to mediate QTc prolongation) was about 100-500 times the plasma level of the sulfone metabolite measured in human plasma.

In the 13-week study in beagle dogs, slight anemia accompanied by minimal increases in reticulocyte and nucleated red cell counts were observed at 39 mg/kg/day (1.1 times the MRHD based on body surface area comparison) predominantly at week 9 of dosing.

14 CLINICAL STUDIES

An open label, randomized trial, conducted in Vietnam compared the efficacy of triclabendazole (two 10 mg/kg doses given 12 hours apart with food) to oral artesunate (4 mg/kg, given once daily for 10 days). One hundred patients (age range: 9-74 years) with acute symptomatic fascioliasis were randomized, 50 in each treatment group. At 3 months after treatment, 92% and 76% (difference 16%; 95% CI [1.7, 30.8], p = 0.035) of patients in the triclabendazole and artesunate arms respectively, reported no clinical symptoms.

The clinical development program of triclabendazole for the treatment of fascioliasis included 6 non-randomized, open label studies performed in Cuba, Bolivia, Peru, Chile, and Iran in a total of 245 adult and pediatric patients with stool-confirmed fascioliasis. All studies were similar in design. The studied triclabendazole doses ranged from 5 mg/kg to 20 mg/kg administered on Days 1-3. Cure was defined as absence of *Fasciola* eggs in the stool based on the Kato-Katz method at Day 60 in patients who were positive at baseline. Across these studies, there was a finding of a dose response. Specifically, the Day 60 cure rate was highest (95.5%; 95% CI [77%, 100%]) for the 20 mg/kg dose, which was given in 2 divided doses, followed by cure rates of 88% (95% CI [64%, 99%]), 80% (95% CI [73%, 86%]), and 50% (95% CI [27%, 73%]) in the 15 mg/kg, 10 mg/kg, and 5 mg/kg dose groups, respectively. The 5 mg/kg, 10 mg/kg, and 15 mg/kg dosing regimens are not approved *[see Dosage and Administration (2)]*. These rates were significantly higher than that estimated from patients receiving an inadequate, non-triclabendazole treatment in a separate study (22%; 95% CI [9.8, 38.2]).

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

EGATEN (triclabendazole) tablets are supplied as pale red, speckled, capsule shaped, biconvex tablets, with imprint “EG EG” on one side and functionally scored on both sides. Each tablet contains 250 mg of triclabendazole. EGATEN (triclabendazole) tablets are available as:

Blister packs of 4 tablets (NDC 0078-0937-91).

Storage

Store in the original container. Store below 30°C (86°F).

17 PATIENT COUNSELING INFORMATION

Important Administration Instructions

Advise patients that EGATEN should be taken orally with food. The tablets can be swallowed whole or divided in half and taken with water, or crushed and administered with applesauce. The crushed tablet mixed with applesauce is stable for up to 4 hours *[see Dosage and Administration (2)]*.

QT Prolongation

Advise patients with a history of prolongation of the QTc interval or a history of symptoms compatible with a long QT interval or when EGATEN is used in patients who receive drugs that prolong the QT interval that their ECGs will need to be monitored *[see Warnings and Precautions (5.1)]*.

Distributed by:

Novartis Pharmaceuticals Corporation

East Hanover, New Jersey 07936

For more information on EGATEN, call 1-888-669-6682.

T2019-100

PRINCIPAL DISPLAY PANEL

Egaten™

(triclabendazole)
Tablets

250 mg

NDC 0078-0937-91

Rx only

4 scored tablets

Novartis

EGATEN

triclabendazole tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0078-0937

Route of Administration	ORAL

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
TRICLABENDAZOLE (UNII: 4784C8E03O) (TRICLABENDAZOLE - UNII:4784C8E03O)	TRICLABENDAZOLE	250 mg

Inactive Ingredients	
Ingredient Name	**Strength**
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
STARCH, CORN (UNII: O8232NY3SJ)	
HYMETELLOSE (4150 MPA.S) (UNII: UVP539BB9Q)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	

Product Characteristics			
Color	RED (Pale red; Speckled)	**Score**	2 pieces
Shape	CAPSULE	**Size**	19mm
Flavor		**Imprint Code**	EGEG
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:0078-0937-91	4 in 1 BLISTER PACK; Type 0: Not a Combination Product	02/13/2019	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA208711	02/13/2019	

Labeler - Novartis Pharmaceuticals Corporation (002147023)

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