Novartis Pharma AG
Basel, Switzerland

# EGATEN®

# Summary of Product Characteristics

| | |
|---|---|
| Author(s): | Ch. Laburte, MD |
| Document status: | Final |
| MPIB approval date | 27 July 2000 |
| Number of pages: | 13 |

Property of Novartis Pharma AG
Confidential
May not be used, divulged, published or otherwise disclosed
without the consent of Novartis Pharma AG

# 1. Name of the medicinal product

EGATEN® 250 mg tablets

# 2. Qualitative and quantitative composition

Active substance: 6-chloro-5- (2,3-dichlorophenoxy) -2-methyl-thiobenzimidazole (triclabendazole).

One tablet contains 250 mg triclabendazole.

For excipients, see 6.1. List of excipients.

# 3. Pharmaceutical form

Tablets

Physical description: Pale red, speckled, capsule shaped, biconvex. One side with imprint "EG EG", the other without imprint but with a score.

# 4. Clinical particulars

## 4.1. Therapeutic indications

Triclabendazole, a benzimidazole derivative, is an anthelmintic with demonstrated activity against trematodes (flukes). It is effective in the treatment of Fascioliasis ("sheep liver fluke infection") caused by *Fasciola hepatica* or *Fasciola gigantica.*

.

## 4.2. Posology and method of administration

The Egaten® tablets are for oral use.

Dosage of triclabendazole should be tailored to the patient's weight. The tablets are scored and divisible into two equal halves in order to facilitate more precise dosing. If the dosage cannot be adjusted accurately, it is recommended to round the dose upward (for example a 40 kg patient would receive 2 whole tablets, i.e., 500 mg = 12.5 mg/kg instead of 10 mg/kg).

Triclabendazole should be administered orally, post-prandially (see 5.2. Pharmacokinetic properties / Influence of food). The tablets can be swallowed or crushed and taken with liquid.

### Posology in adults

10 mg/kg body-weight as a single dose.

Concomitant treatment with antispasmodics has been shown to reduce pain and minimise the risk of jaundice.

### Posology in children 6 years of age and older

Although the clinical data are limited in this population, there was no evidence of differences between adults and children in efficacy or safety. Posology and treatment schedule should be the same as for adults.

As there may be considerable disproportion between parasite size and biliary tract of children, concomitant antispasmodic therapy should be considered regularly.

### Severe and chronic infection resistant to previous anthelmintic treatment in adults and children older than 15 years

A dose of 20 mg/kg body-weight given in two divided doses 12-24 hours apart was administered to such patients without indication of increased toxicity.

### Children below 6 years of age

There is no experience with triclabendazole treatment in this population.

### Elderly patients

No information is available on the relationship between age and the effects of triclabendazole in elderly patients.

### Patients with renal impairment

As no studies have been carried out in patients with renal impairment, no recommendations can be made for this population.

### Patients with liver impairment

No studies have been performed in patients with liver impairment. Nevertheless, in the clinical studies, a large proportion of patients had abnormal pre-treatment liver function tests (aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), alkaline phosphatase and the total bilirubin) which either normalised or remained stable following treatment. The most common new abnormality following treatment was a high serum alkaline phosphatase indicating probably a functional cholestasis. In some cases increased bilirubin and/or transaminase levels accompanied the alkaline phosphatase increases. It seems likely that the liver function tests abnormalities seen at baseline were due to fascioliasis, and that the predominantly cholestatic type abnormalities observed following treatment may be the result of the expulsion of flukes through the biliary tree. This is supported by the rarity of such changes in patients treated for paragonimiasis.

Based on this data, triclabendazole should be administered with caution in patients with liver impairment not related to fascioliasis. In these patients, the treating physician should weigh the expected therapeutic benefit against the potential risks.

## 4.3. Contraindications

Hypersensitivity to triclabendazole and or to other benzimidazole derivatives or to any of the excipients.

For use during pregnancy and lactation see 4.6.

## 4.4. Special warnings and special precautions for use

There is no experience with triclabendazole treatment in children below 6 years of age.

Mild to moderate transient increases in serum concentrations of liver enzymes (ASAT, ALAT, alkaline phosphatase) and in total bilirubin have been reported in some patients receiving triclabendazole and in animals (see 4.2. Posology and method of administration "Patients with liver impairment" and 5.3. Preclinical safety data). The drug should therefore be used with caution in patients with pre-existing liver dysfunction.

No data are available for patients with renal impairment, and no treatment recommendations can be made for this population.

ECG recordings in dogs indicated prolongation of QT and/or QTc intervals in 3 of 10 animals at 40mg/kg single dose administration and in 4 of 10 animals at 100 mg/kg single dose administration, probably related to the sulfone metabolite (see 5.3 Preclinical safety data / Repeated dose toxicity). There have been no reports of faint, syncope or acute cardiac incidents in the 818 patients treated with triclabendazole in the clinical trials or in the other numerous published cases. Nevertheless triclabendazole should be used with caution in patients with known QT prolongation, cardiac conduction disorders, arrhythmias or a history of such conditions.

Coadministration of Egaten and drugs primarily metabolised by the cytochrome P450 enzymes may result in increased plasma concentrations of the other drugs (see 4.5. Interactions with other medicinal products and other forms of interaction). Therefore, discontinuation of concomitant medications metabolised by the cytochrome P450 1A2, 2C9 or 3A4 enzymes, or monitoring of plasma concentrations of these co-medications may be necessary. Triclabendazole should be used with caution in patients with glucose-6-phosphate dehydrogenase deficiency due to the possibility to induce hemolysis.

## 4.5. Interactions with other medicinal products and other forms of interaction

None known *in vivo* for triclabendazole itself.

*In vitro*, triclabendazole and its major active sulfoxide metabolite are inhibitors of the cytochrome P450 1A2, 2C9 and/or 3A4 isoenzymes. Coadministration of triclabendazole and drugs primarily metabolised by these cytochrome P450 enzymes may result in increased plasma concentrations of the other drugs.

Therefore, discontinuation of concomitant medications metabolised by the cytochrome P450 1A2, 2C9 or 3A4 enzymes, or monitoring of plasma concentrations of these co-medications may be necessary.

### Class interactions (other benzimidazoles)

Thiabendazole may compete with other drugs (e.g. theophylline) for sites of metabolism in the liver and thereby increase serum concentrations of such drugs to potentially toxic levels.

When thiabendazole and a xanthine derivative are used concomitantly, it may be necessary to monitor serum concentrations of the xanthine derivative and/or reduce its dosage.

However, it should be kept in mind that the risk would probably be minimal in view of the single dose administration and the short half-life (11-17 hours) of the compound.

No specific drug interaction studies have been conducted with triclabendazole in human; however, formal animal studies with triclabendazole in combination with other anthelmintics such as fenbendazole or levamisole have shown no pharmacokinetic interaction and no evidence of synergistic toxicity.

## 4.6. Use during pregnancy and lactation

### Pregnancy

Studies in rats and rabbits (see 5.3. Preclinical Safety Data) have not revealed evidence of harm to the foetus, although birth weight was lower in the offspring of animals given doses of 100 and 200 mg/kg body weight/day, which are equivalent to 10 to 20 times the recommended therapeutic dose in humans for the more usual treatment.

Other benzimidazole derivatives such as mebendazole, oxfendazole, flubendazole and albendazole, have been shown to be embryotoxic and teratogenic in some species of laboratory animals.

This difference in embryotoxicity and teratogenicity potential could be related to the different mode of action of triclabendazole as compared to other benzimidazole anthelmintics (see 5.1. Pharmacodynamic properties “Mechanisms of action”).

Nevertheless, in the absence of appropriate controlled studies in pregnant women, triclabendazole should be used in pregnancy only when the potential benefits outweigh the possible risks.

### Lactation

Transfer of radioactive substance(s) into the rat embryo/foetal compartments was investigated following single peroral administration of $^{14}C$-labelled triclabendazole at a dose of 10 mg/kg. Excretion into the milk of lactating rats was not specifically investigated. However, as a result of the uptake of radioactivity into the mammary

glands, the triclabendazole may well be excreted with the milk in lactating animals. Published data indicate that in goats, approximately 1% of an oral dose is excreted in the milk.

Since no information on drug concentrations in milk is available for humans, triclabendazole should be avoided during lactation. Nevertheless if lactation must be continued, it should be suspended during treatment and for the following 72 hours.

## 4.7. Effects on ability to drive and use machines

Patients should be warned that dizziness might occur, in which case they should not drive, operate potentially dangerous machinery, or engage in other activities that may become hazardous.

## 4.8. Undesirable effects

*Frequency estimates: very common ≥10%, common ≥1% to <10%; uncommon ≥ 0.1% to <1%; rare ≥0.01% to <0.1%; very rare <0.01%.*

It should be kept in mind that some adverse events associated with triclabendazole treatment may be secondary to the parasitic infection being treated, to dying parasites and/or to expulsion of dead parasites from the hepatobiliary system rather than to the drug itself. Such effects may be more frequent and/or severe in patients with a heavy worm burden.

### Body as a whole

Very common: sweating

Common: weakness, chest pain, fever

### Digestive system

Very common: abdominal/epigastric pain

Common: anorexia, diarrhoea, nausea, vomiting

### Liver/biliary system

Common: icterus/jaundice, biliary colic

### Nervous system

Common: dizziness/vertigo, headache

Uncommon: drowsiness

### Skin

Common: urticaria,

Uncommon: pruritus

#### Musculo-skeletal system

Uncommon: back pain

#### Respiratory

Common: dyspnea, cough

#### Renal / metabolic disorders

Uncommon: borderline and reversible elevations of serum creatinine.

## 4.9. Overdose

No specific information is available either on the clinical signs and symptoms or on the treatment of overdose with triclabendazole.

# 5. Pharmacological properties

## 5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Anthelmintic, antitrematodal agent (ATC code: PO2B X)

### Spectrum

The antiparasitic spectrum of triclabendazole is characterised by specific activity against early immature, immature and adult flukes of *Fasciola hepatica* and *F. gigantica* in both domestic animals and humans. Triclabendazole is effective against flukes as early as 24 hours after infection, as well as at the pre-pathogenic (weeks 1 to 4 after infection), acute, subacute and chronic stages of the disease.

Activity has also been demonstrated in lung fluke infections due to *Paragonimus uterobilateralis* in infected cotton rats, and due to *P. uterobilateralis*, *P. africanus*, *P. mexicanus* and *P. westermani* in humans.

### Mechanisms of action

The exact mechanisms of action of triclabendazole and of its main active sulfoxide metabolite against trematodes have not been fully elucidated.

Although this drug can be chemically considered as a benzimidazole derivative, its structural characteristics (presence of chlorine atoms and a thiomethyl group, absence of carbamate moiety) clearly differentiate it from all other benzimidazole anthelmintics. Lack of nematocidal activity also suggests that it is acting differently from all other benzimidazole anthelmintics, which irreversibly inhibit glucose uptake by susceptible worms and slowly killing them by depleting their energy sources (glycogen and adenosine triphosphate). In addition, no uncoupling activity characteristic of classic anthelmintic fasciolicidal salicylanides has been found. The only information available at present is that triclabendazole and its active sulfoxide metabolite readily penetrate the tegument of the fluke, rapidly inhibit its motility

and interfere with its microtubular structure and function. The sulfoxide metabolite was found to exert a delayed, but more potent effect on parasite motility than triclabendazole itself. Thus, it is likely that the drug acts mainly through its sulfoxide metabolite, which is largely predominant in human plasma. In addition, as the drug inhibits colchicine binding to purified liver fluke tubulin, it alters the resting membrane potential and prevents proteolytic enzyme release from mature and immature worms.

No general pharmacological studies have been undertaken in mammalian species. No effects on smooth muscle or the cardiovascular, respiratory or nervous systems were detected in the various toxicity studies. Specifically, no effect on action potential duration was observed in the rabbit Purkinje fibre model at clinically relevant concentrations.

## 5.2. Pharmacokinetic properties

Extensive referenced summaries of relevant animal studies are available.

In humans, pharmacokinetic investigations rely mostly on the plasma concentrations of the sulfoxide metabolite, since biotransformation of triclabendazole to its metabolite in the systemic circulation is rapid and nearly complete. Only minute amounts of unchanged compound can be detected in humans. Simultaneous determinations of triclabendazole and its sulfoxide and sulfone metabolites were performed using HPLC.

### Absorption

Following oral administration of 10 mg/kg triclabendazole to fasting patients, absorption was rapid with a median $t_{max}$ for both the parent compound and the sulfoxide metabolite of 2 hours. Mean peak plasma concentrations for triclabendazole and the sulfoxide metabolite were 0.34 and 15.8 μmol/L, respectively, with respective AUCs of 1.55 and 177 μmol.h/L.

### Distribution

The apparent volume of distribution of the sulfoxide metabolite in fed patients is about 1 L/kg (assuming complete drug absorption and complete conversion of triclabendazole to the sulfoxide metabolite).

Protein binding in human is 96.7% for triclabendazole, 98.4-99.7% for the sulfoxide metabolite and ≥ 99.5% for the sulfone metabolite.

Studies in sheep and human plasma suggest that the binding (99%) is mainly to albumin, with only low circulating concentrations of free active compounds.

### Metabolism

*In vivo*, triclabendazole is rapidly oxidised into its sulfoxide metabolite, which is further oxidised to the sulfone metabolite. The sulfoxide form is predominant in plasma, with the parent compound and the sulfone metabolite having AUCs

respectively of approximately 1% and 10% of that of the sulfoxide. The rapid biotransformation of triclabendazole in man and the previous findings in animals produced evidence of presystemic biotransformation including first-pass metabolism of triclabendazole.

### Excretion

In animals**,** the drug is largely excreted via the biliary tract in the faeces (90%), together with the sulfoxide and subsequently the sulfone metabolite. Less than 10% of an oral dose is excreted in the urine.

The elimination half-life of the sulfoxide metabolite from plasma is about 11 hours. Similar terminal phases of log-linear decreases in concentrations were observed for the three compounds under both fasted and fed conditions.

### Influence of food

The influence of food on the pharmacokinetics of triclabendazole and its metabolites has been investigated in patients after oral administration of a 10 mg/kg dose. An increase in systemic availability, probably due to improved gastro-intestinal absorption, has been observed following administration of triclabendazole under fed conditions. $T_{max}$, $C_{max}$ and AUC were at least doubled for the sulfoxide. Substantial increases in these parameters were also observed for the parent compound. The pharmacokinetics of the minor sulfone metabolite was influenced by food in the same way.

To improve the systemic availability of the compound and its metabolites, administration of triclabendazole with food is therefore recommended.

### Influence of gender

Marginal influence of gender has been detected.

### Pharmacokinetics in special patient populations

No specific studies were undertaken in special patient populations. However, 7 of the 20 patients included in the pharmacokinetic study were children aged 9-15 years. AUC values were somewhat lower in these patients than in the other 13 patients, but the difference was not statistically significant and all children were cured by the treatment. No information is available on pharmacokinetics in the elderly, or in patients with renal or severe hepatic impairment.

## 5.3. Preclinical safety data

### Acute toxicity

In single-dose toxicity studies, triclabendazole was given orally (mice, rats, rabbits), intradermally (rat), intraperitoneally (rat) or by inhalation (rat).

The oral $LD_{50}$ for triclabendazole is estimated to range from > 8000 mg/kg (mice and rats) to 206 mg/kg (rabbits). The corresponding doses for the two major metabolites (sulfoxide and sulfone) are estimated in rats to be > 5000 mg/kg.

## Repeated dose toxicity

Triclabendazole was administered to rats and beagle dogs, in the diet at doses of 10, 100 and 1000 ppm daily, for 13 weeks.

There were no evidence of dose-related mortality and no major toxicological changes in the rat study.

However, in the dog study (n = 12 per dose group), albeit at the highest dose level of 1000 ppm (corresponding to a dose of 39 mg/kg body-weight), non-specific weight loss was noted. In addition, a marginal increase in QT intervals was reported in the ECG recordings (QT of 0.24 s in 4 dogs and of 0.26 s in one single dog at weeks 5 and 9; QTnormal range: 0.19- 0.23 s). In order to investigate this finding triclabendazole was administered to beagle dogs at single doses of 40 or 100 mg/kg. Electrocardiographic examinations showed prolongation of QT and/or QTc intervals in 3 of 10 animals at 40 mg/kg (one clearly, two marginally) and 4 of 10 animals at 100 mg/kg (two clearly, two marginal) in the 24-hour and partly also in the 48-hour recordings. The study data indicated that the sulfone metabolite was most likely responsible for QT/QTc prolongation in the dogs as the time points of this finding correlate well with peak concentrations of the sulfone metabolite, especially in the affected dogs. As the sulfone metabolite occurs at very low concentrations in humans, it is very unlikely that it would cause QT interval prolongation in patients.

In both species (rats and beagle dogs), at the highest dose level anaemia accompanied by the usual rises in reticulocyte and nucleated red cell counts was observed. This was due to the production of methemoglobin by the sulfone metabolite of triclabendazole.

The NOEL was 0.7 to 0.8 mg/kg body weight in rats (10 ppm) and 0.35 mg/kg body weight in dogs (10 ppm).

## Reproduction toxicity

No drug-related effects on reproductive performance, mating ratios or fertility indices have been noted.

## Embryotoxicity and teratogenicity studies

No evidence of a teratogenic potential has been noted in any of the studies performed (rats and rabbits).

The highest dose tested in an additional study in rats, published in the literature, was equivalent to over 20 times the recommended therapeutic dose in man for the more usual routine treatment. The only foetal effect reported in this study was reduced body-weight at 100 and 200 mg/kg body weight/day.

### Mutagenicity

Negative results have been obtained in a battery of six tests (reverse and forward mutations, unscheduled DNA synthesis, nuclear anomalies, sister chromatid exchange and two *in vivo* experiments).

### Carcinogenicity/long-term toxicity studies

Two-year studies in mice and rats (receiving triclabendazole at doses up to three times the normal human dose) have shown no carcinogenic potential.

In mice, serum levels of alkaline phosphatase and hepatic transaminases (ASAT, ALAT) were increased in high-dosed animals in the first year and (with marginal significance) in all treated animals during the second year. At necropsy, there were no abnormal findings at one year. At two years, liver weight was significantly increased in all but the lowest dosed animals, and the incidence of benign hepatic adenomas approximately doubled in three of four groups of treated females.

The hepatotrophic effect demonstrated by increased liver weights, enzyme levels and benign tumours (hepatomas), could be considered to be a non-specific response to the administration of a xenobiotic, and as such reflects similar changes that have been seen with many other entirely unrelated substances.

The results from this study were very favourable for triclabendazole and none of the liver changes, albeit non-specific, seen in mice were noted in rats after oral dietary administration for 104 weeks; the only treatment related effect was a slight reduction in body weight gain in both sexes at 100 ppm.

The NOEL daily intakes were 1.56 mg/kg in mice, 1.2 mg/kg in male rats and 1.5 mg/kg in female rats.

# 6. Pharmaceutical particulars

## 6.1. List of excipients

Lactose monohydrate, maize starch, methylcellulose 50 cP, magnesium stearate, colloidal silicon dioxide, iron oxide red.

## 6.2. Incompatibilities

None known.

## 6.3. Shelf life

Three years.

## 6.4. Special precautions for storage

Protect from light.

Store in the original container. Do not store above 25°C.

The preparation should not be used after the date marked "EXP" on the folding box.

## 6.5. Nature and content of container

PVC/PE/PVDC blister pack consisting of

- a cover foil (aluminium foil thermolacquered on one side and with a protective layer of lacquer on the other side).
- a bottom foil (laminated plastic film made of polyvinylchloride, polyethylene and polyvinylidenchloride).

Box of 4 or 100 Egaten scored tablets.

## 6.6. Instructions for use and handling, and disposal (if appropriate)

No specific instructions for use/handling.

# 7. Marketing authorisation holder

Novartis Pharma AG.

# 8. Number(s) in the Community Register of Medicinal Products

# 9. Date of first authorisation/renewal of the authorisation

# 10. Date of revision of the text