MECURE INDUSTRIES PLC

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

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1. Name of the Medicinal Product

Evikt Tablets

2. Qualitative and Quantitative Composition

Levamisole 40mg, film coated tablets

1 film coated tablet contains: 40mg Levamisole (as Levamisole Hydrochloride)

For excipients see 6.1

3. Pharmaceutical Form

Film-coated tablet
Pink circular, biconvex, film coated tablets

4. Clinical Particulars

4.1. Therapeutic Indications

EVIKT (levamisole hydrochloride) is very effective against ascaris lumbricoides and is generally considered as the drug of choice. **EVIKT** is indicated as adjuvant treatment in combination with fluorouracil after surgical resection in patients with Dukes' stage C colon cancer.

4.2. Posology and method of administration

Route of administration: By mouth (oral).
In adults, it is given as a single dose of 120 – 150 mg preferably after a light meal.

Age	Dosage
1-4	1
5-15	2
16 and over	3

4.3. Contra-Indications

EVIKT (levamisole hydrochloride) is contraindicated in patients with a known hypersensitivity to the drug or its components.

4.4. Special warnings and precautions for use

In case of concurrent microfilaraemia transient fever may occur.

4.5. Interaction with other medicinal products and other forms of interaction

No known interactions with other medicaments**.**

4.6. Pregnancy and Lactation

EVIKT do have any Teratogenecity effect.

4.7. Effects on the ability to drive and use machines

There is no evidence to suggest that levamisole used for anithelmintic purposes will produce sedation. Mild and transient giddiness (dizziness) is an infrequent side effect of treatment. No precautions are suggested concerning the ability to drive or operate machinery.

4.8. Undesirable effects

Almost all patients receiving **EVIKT** (levamisole hydrochloride) and fluorouracil reported adverse experiences. Tabulated below is the incidence of adverse experiences that occurred in at least 1% of patients enrolled in two clinical trials who were adjuvantly treated with either **EVIKT** or EVIKT plus fluorouracil following colon surgery. In the larger clinical trial, 66 of 463 patients (14%) discontinued the combination of EVIKT plus fluorouracil because of adverse reactions. Forty-three of these patients (9%) developed isolated or a combination of gastrointestinal toxicities (e.g. nausea, vomiting, diarrhea, stomatitis and anorexia). Ten patients developed rash and/or pruritus. Five patients discontinued therapy because of flu-like symptoms or fever with chills; ten patients developed central nervous system symptoms such as dizziness, ataxia, depression, confusion, memory loss, weakness, inability to concentrate, and headache; two patients developed reversible neutropenia and sepsis; one patient because of thrombocytopenia; one patient because of hyperbilirubinemia. One patient in the EVIKT plus fluorouracil group developed agranulocytosis and sepsis and died.

In the EVIKT alone arm of the trial, 15 of 310 patients (4.8%) discontinued therapy because of adverse experiences. Six of these (2%) discontinued because of rash, six because of arthralgia/myalgia, and one each for fever and neutropenia, urinary infection, and cough.

Adverse experience	**EVIKT N = 440** %	**EVIKT plus fluorouracil N = 599** %
Gastrointestinal		
Nausea	22	65
Diarrhea	13	52
Stomatitis	3	39
Vomiting	6	20
Anorexia	2	6
Abdominal pain	2	5
Constipation	2	3

Flatulence	<1	2
Dyspepsia	<1	1
Hematological		
Leukopenia		
< 2000/mm^3	<1	1
2000 to < 4000/mm^3	4	19
4000/mm^3	2	33
unscored category	0	<1
Thrombocytopenia		
< 50,000/ mm^3	0	0
50, 000 to < 130,000/mm^3	1	8
130,000/mm^3	1	10
Anemia	0	6
Granulocytopenia	<1	2
Epistaxis	0	1
Skin and Appendages		
Dermatitis	8	23
Alopecia	3	22
Pruritus	1	2
Skin discoloration	0	2
Urticaria	<1	0
Body as a Whole		
Fatigue	6	11
Fever	3	5

Rigors	3	5
Chest pain	<1	1
Edema	1	1
Resistance Mechanisms		
Infection	5	12
Special Senses		
Taste Perversion	8	8
Altered sense of smell	1	1
Musculoskeletal System		
Arthralgia	5	4
Myalgia	3	2
Central and peripheral nervous system		
Dizziness	3	4
Headache	3	4
Paresthesia	2	3
Ataxia	0	2
Psychiatric		
Somnolence	3	2
Depression	1	2
Nervousness	1	2
Insomnia	1	1
Anxiety	1	1
Forgetfulness	0	1
Vision		
Abnormal tearing	0	4

Blurred vision	1	2
Conjunctivitis	<1	2
Liver and biliary system		
Hyperbilirubinemia	<1	1

In worldwide experience with EVIKT, less frequent adverse experiences included exfoliative dermatitis, fixed drug eruptions, periorbital edema, vaginal bleeding, anaphylaxis, confusion, convulsions, hallucinations, impaired concentration, renal failure, pancreatitis, elevated serum creatinine, and increased alkaline phosphatase.

Reports of hyperlipidemia have been observed in patients receiving combination therapy of EVIKT and fluorouracil; elevations in triglyceride levels have been greater than increases in cholesterol levels. In worldwide postmarketing experience with the combination therapy, there have been rare cases of elevated hepatic enzymes and hepatosteatosis in patients.

The following additional adverse experiences have been reported for fluorouracil alone: esophagopharyngitis, pancytopenia, myocardial ischemia, angina, gastrointestinal ulceration and bleeding, anaphylaxis and generalized allergic reactions, acute cerebellar syndrome, nystagmus, dry skin, fissuring, photosensitivity, lacrimal duct stenosis, photophobia, euphoria, thrombophlebitis, and nail changes.

4.9. Overdose

Counter possible anticholinesterase activity with Atropine. Control blood pressure and respiration. Do not give sedatives.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Two clinical trials having essentially the same design have demonstrated an increase in survival and a reduction in recurrence rate in the subset of patients with resected Dukes' C colon cancer treated with a regimen of EVIKT®, (levamisole hydrochloride) plus fluorouracil.[1,2] After surgery, patients were randomized to no further therapy, EVIKT® alone, or EVIKT® plus fluorouracil.

In one clinical trial in which 408 Dukes' B and C colorectal cancer patients were studied, 262 Dukes' C patients were evaluated for a minimum follow-up of five years.[1] A subset analysis of these Dukes' C patients showed the estimated reduction in death rate was 27% for EVIKT® plus fluorouracil ($p = 0.11$) and 28% for EVIKT® alone ($p = 0.11$).[3] The estimated reduction in recurrence rate was 36% for EVIKT® plus fluorouracil ($p = 0.025$) and 28% for EVIKT® alone ($p = 0.11$).[3] In another clinical trial designed to confirm the above results, 929 Dukes' C colon cancer patients were evaluated for a minimum follow-up of 2 years.[2] The estimated reduction in death rate was 33% for EVIKT® plus fluorouracil ($p = 0.006$). The estimated reduction in recurrence rate was 41% for EVIKT® plus fluorouracil, ($p < 0.0001$). The EVIKT® alone group did not show advantage over no treatment on improving recurrence or survival rates. There are presently insufficient data to evaluate the effect of the combination of EVIKT® plus fluorouracil

in Dukes' B patients. There are also insufficient data to evaluate the effect of EVIKT® plus fluorouracil in patients with rectal cancer because only 12 patients with rectal cancer were treated with the combination in the first study and none in the second study.

The mechanism of action of EVIKT® in combination with fluorouracil is unknown. The effects of levamisole on the immune system are complex. The drug appears to restore depressed immune function rather than to stimulate response to above-normal levels. Levamisole can stimulate formation of antibodies to various antigens, enhance T-cell responses by stimulating T-cell activation and proliferation, potentiate monocyte and macrophage functions including phagocytosis and chemotaxis, and increase neutrophil mobility, adherence, and chemotaxis. Other drugs have similar short-term effects and the clinical relevance is unclear.

Besides its immunomodulatory function, levamisole has other mammalian pharmacologic activities, including inhibition of alkaline phosphatase, and cholinergic activity.

5.2 Pharmacokinetic properties

The pharmacokinetics of EVIKT® have not been studied in the dosage regimen recommended with fluorouracil. After administration of a single oral dose of 50 mg of a research formulation of EVIKT®, it appears that levamisole is rapidly absorbed from the gastrointestinal tract. Mean peak plasma concentrations of 0.13 mcg/ml are attained within 1.5 to 2 hours. The plasma elimination half-life of levamisole is between 3-4 hours. Following a 150-mg radio-labeled dose, levamisole is extensively metabolized by the liver in humans and the metabolites excreted mainly by the kidneys (70% over 3 days). The elimination half-life of metabolite excretion is 16 hours. Approximately 5% is excreted in the feces. Less than 5% is excreted unchanged in the urine and less than 0.2% in the feces. Approximately 12% is recovered in the urine as the glucuronide of p-hydroxy-levamisole. The clinical significance of these data are unknown since a 150-mg dose may not be proportional to a 50-mg dose. In the presence of cirrhosis in twelve patients with alcoholic cirrhosis and hepatitis, the C_{max} of EVIKT® was not clearly increased, but the AUC was 1 to 20-fold increased compared to normal volunteers.

5.3 Preclinical safety data

Not available

6. Pharmaceutical particulars

6.1 List of excipients

Tablet core:

Maize Starch
Lactose
Propyl Paraben
Methyl Paraben
Isopropyl Alcohol
P. v. P. K30
Methylene Chloride
Magnesium Stearate
Talcum

Aerosil
Sodium Starch Glycolated

Film coating:

Isopropyl Alcohol
Ready Coat Material (Lake Ponceau 4R)
Methylene Chloride

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store in a cool dry place at temperature below 30°C. Store in the original packaging.

6.5 Nature and contents of container

Plastic Jar pack containing 500 coated tablet

6.6 Special precautions for disposal and other handling

None.

7. Marketing authorization holder

Me Cure Industries Limited

Plot 6 Block H, Debo Industries Compound,

Oshodi Industrial Scheme,

Oshodi,

Lagos,

Nigeria.

8.0 NAFDAC Registration Number: A4-0210