Trifluxen
(Trifluridine and Tipiracil) tablets

Everest

COMPOSITION
Trifluxen tablet: Each film coated tablet contains Trifluridine BP 15 mg and Tipiracil Hydrochloride INN equivalent to Tipiracil 6.14 mg.

PHARMACOLOGY
Mechanism of Action
Trifluridine and Tipiracil consists of a thymidine-based nucleoside analog, Trifluridine, and the thymidine phosphorylase inhibitor, tipiracil, at a molar ratio 1:0.5 (weight ratio, 1:0.471). Inclusion of Tipiracil increases Trifluridine exposure by inhibiting its metabolism by thymidine phosphorylase.

Following uptake into cancer cells, Trifluridine is incorporated into DNA, interferes with DNA synthesis and inhibits cell proliferation. Trifluridine/Tipiracil demonstrated anti-tumor activity against KRAS wild-type and mutant human colorectal cancer xenografts in mice.

Pharmacokinetic Properties
After twice daily dosing of Trifluridine and Tipiracil, systemic exposure (AUC) of trifluridine increased more than dose-proportionally over the dose range of 15 mg/m^2 (0.43 times the recommended dose) to 35 mg/m^2.

The accumulation of Trifluridine was 3-fold for $AUC_{0\text{-}12hr}$ and 2-fold for C_{max} at steady state while no accumulation was observed for tipiracil.

Administration of a single dose of Trifluridine and Tipiracil 35 mg/m^2 increased the mean $AUC_{0\text{-}last}$ of Trifluridine by 37-fold and C_{max} by 22-fold with reduced variability compared to administration of a single dose of trifluridine 35 mg/m^2 alone.

Absorption
Following a single oral administration of Trifluridine and Tipiracil at 35 mg/m^2 in patients with cancer, the mean time to peak plasma concentration (T_{max}) of Trifluridine was around 2 hours.

Food Effect
A standardized high-fat, high-calorie meal decreased Trifluridine C_{max}, Tipiracil C_{max} and AUC by approximately 40%, but did not change Trifluridine AUC compared to those in a fasting state in patients with cancer following administration of a single dose of Trifluridine and Tipiracil 35 mg/m^2.

Distribution
Trifluridine mainly binds to human serum albumin. The in vitro protein binding of Trifluridine in human plasma is >96%, independent of drug concentration and presence of Tipiracil. Plasma protein binding of Tipiracil is below 8%.

Elimination
After administration of Trifluridine and Tipiracil 35 mg/m^2, the mean elimination half-life ($t_{1/2}$) of Trifluridine was 1.4 hours and of Tipiracil was 2.1 hours after a single dose. The mean elimination half-life at steady state of Trifluridine was 2.1 hours and of Tipiracil was 2.4 hours.

Metabolism
Trifluridine and Tipiracil are not metabolized by cytochrome P450 (CYP) enzymes. Trifluridine is mainly eliminated by metabolism via thymidine phosphorylase to form an inactive metabolite, 5-(Trifluoromethyl) uracil (FTY). No other major metabolites were detected in plasma or urine.

Excretion
After single oral administration of Trifluridine and Tipiracil (60 mg) with [14C]-trifluridine, the total cumulative excretion of radioactivity was 60% of the administered dose. The majority of recovered radioactivity was eliminated into urine (55% of the dose) as FTY and trifluridine glucuronide isomers within 24 hours and the excretion into feces and expired air was <3% for both. The unchanged trifluridine was <3% of administered dose recovered in the urine and feces.

After single oral administration of Trifluridine and Tipiracil (60 mg) with [14C]-Tipiracil hydrochloride, recovered radioactivity was 77% of the dose, which consisted of 27% urinary excretion and 50% fecal excretion. Tipiracil was the major component and 6-HMU was the major metabolite in urine, and feces.

Specific Populations
Based on the population pharmacokinetic analysis, there is no clinically relevant effect of age, sex, or race (White or Asian) on the pharmacokinetics of trifluridine or tipiracil.

Patients with Renal Impairment
In a dedicated renal impairment study, all patients received Trifluridine and Tipiracil 35 mg/m^2 twice daily except for patients with severe renal impairment who received 20 mg/m^2 twice daily. Mild renal impairment (CLcr of 60 to 89 mL/min as determined by the Cockcroft-Gault formula) had no clinically important effect on steady-state $AUC_{0\text{-}last}$ of trifluridine and tipiracil. Moderate renal impairment (CLcr of 30 to 59 mL/min) increased steady-state $AUC_{0\text{-}last}$ of Trifluridine by 56% and Tipiracil by 139% compared to normal renal function (CLcr ≥ 90 mL/min). Severe renal impairment (CLcr of 15 to 29 mL/min) increased the dose-normalized steady-state $AUC_{0\text{-}last}$ of Trifluridine by 140% and Tipiracil by 614% compared to normal renal function. The pharmacokinetics of Trifluridine and Tipiracil have not been studied in patients with end stage renal disease.

Patients with Hepatic Impairment
No clinically important differences in the mean exposures of Trifluridine and Tipiracil were observed between patients with mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN or total bilirubin <1 to 1.5 times ULN and any AST) to moderate hepatic impairment (total bilirubin >1.5 to 3 times ULN and any AST) and patients with normal hepatic function (total bilirubin and AST ≤ ULN); however, 5 of 6 patients with moderate hepatic impairment experienced Grade 3 or 4 increased bilirubin levels. The pharmacokinetics of Trifluridine and Tipiracil have not been studied in patients with severe hepatic impairment.

Drug Interaction Studies
In vitro studies indicated that Trifluridine, Tipiracil, and FTY did not inhibit the CYP enzymes and had no inductive effect on CYP1A2, CYP2B6, or CYP3A4/5.

In vitro studies indicated that Trifluridine was not an inhibitor of or substrate for human uptake and efflux transporters.

INDICATIONS AND USAGE
Metastatic Colorectal Cancer
Trifluridine and Tipiracil is indicated for the treatment of adult patients with metastatic colorectal cancer previously treated with fluoropyrimidine, oxaliplatin-and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy.

Metastatic Gastric Cancer
Trifluridine and Tipiracil is indicated for the treatment of adult patients with metastatic gastric or gastroesophageal junction adenocarcinoma previously treated with at least two prior lines of chemotherapy that included a fluoropyrimidine, a platinum, either a taxane or irinotecan, and if appropriate, HER2/neu-targeted therapy.

DOSAGE AND ADMINISTRATION

Recommended Dosage
The recommended dosage of Trifluridine and Tipiracil is 35 mg/m^2 up to a maximum of 80 mg per dose (based on the Trifluridine component) orally twice daily with food on Days 1 through 5 and Days 8 through 12 of each 28-day cycle until disease progression or unacceptable toxicity. Round dose to the nearest 5 mg increment.

Instruct patients to swallow the tablet whole.

Instruct patients not to retake doses of Trifluridine and Tipiracil that are vomited or missed and to continue with the next scheduled dose.

Trifluridine and Tipiracil is a cytotoxic drug. Follow applicable special handling and disposal procedures.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Severe Myelosuppression
In the 868 patients who received Trifluridine and Tipiracil in RECOURSE and TAGS, Trifluridine and Tipiracil caused severe and life-threatening myelosuppression (Grade 3-4) consisting of anemia (18%), neutropenia (38%), thrombocytopenia (5%) and febrile neutropenia (3%). Two patients (0.2%) died due to neutropenic infection/sepsis and four other patients (0.5%) died due to septic shock. A total of 12% of Trifluridine and Tipiracil-treated patients received granulocyte-colony stimulating factors.

Obtain complete blood counts prior to and on Day 15 of each cycle of Trifluridine and Tipiracil and more frequently as clinically indicated. Withhold Trifluridine and Tipiracil for severe myelosuppression and resume at the next lower dosage.

Embryo-Fetal Toxicity
Based on animal studies and its mechanism of action, Trifluridine and Tipiracil can cause fetal harm when administered to a pregnant woman. Trifluridine/tipiracil caused embryo-fetal lethality and embryo-fetal toxicity in pregnant rats when orally administered during gestation at dosage levels resulting in exposures lower than those achieved at the recommended dosage of 35 mg/m^2 twice daily. Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use an effective method of contraception during treatment with Trifluridine and Tipiracil and for at least 6 months after the final dose.

SIDE EFFECTS

The most common adverse reactions or laboratory abnormalities (≥10%) are anemia, neutropenia, fatigue/asthenia, nausea, thrombocytopenia, decreased appetite, diarrhea, vomiting, and pyrexia.

DRUG INTERACTIONS STUDIES

In vitro studies indicated that Trifluridine, Tipiracil, and FTY did not inhibit the CYP enzymes and had no inductive effect on CYP1A2, CYP2B6, or CYP3A4/5.

In vitro studies indicated that Trifluridine was not an inhibitor of or substrate for human uptake and efflux transporters.

USE IN SPECIFIC POPULATIONS

Pregnancy
Based on animal data and its mechanism of action Trifluridine and Tipiracil can cause fetal harm.

Lactation
There are no data on the presence of Trifluridine, Tipiracil or its metabolites in human milk or its effects on the breastfed child or on milk production.

Females and Males of Reproductive Potential
Pregnancy Testing
Verify pregnancy status in females of reproductive potential prior to initiating Trifluridine and Tipiracil.

Contraception
Trifluridine and Tipiracil can cause fetal harm when administered to a pregnant woman.

Females
Advise females of reproductive potential to use effective contraception during treatment with Trifluridine and Tipiracil and for at least 6 months after the final dose.

Males
Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use condoms during treatment with Trifluridine and Tipiracil and for at least 3 months after the final dose.

Pediatric Use
Safety and effectiveness of Trifluridine and Tipiracil in pediatric patients have not been established.

Geriatric Use
No overall differences in effectiveness were observed in patients 65 or older versus younger patients.

Renal Impairment
No dose adjustment is recommended for patients with mild or moderate renal impairment (CLcr of 30 to 89 mL/min as determined by the Cockcroft-Gault formula). Reduce the dose of Trifluridine and Tipiracil for patients with severe renal impairment (CLcr of 15 to 29 mL/min). The pharmacokinetics of Trifluridine and Tipiracil have not been studied in patients with end stage renal disease.

PHARMACEUTICAL INFORMATION

Storage Condition
Store below 30°C, in a cool and dry place. Keep away from light. Keep out of the reach of children.

HOW SUPPLIED

Trifluxen tablet: Each HDPE container contains 30 Tablets (Trifluridine 15 mg and Tipiracil 6.14 mg) a silica gel desiccant and polyester coil with a child- resistant closure.

Manufactured by
Everest Pharmaceuticals Ltd.
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