Tipanat® 40500072 40500072 Tipanat®

Trifluridine and Tipiracil Tablets

Tipanat®
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1. Generic Name:
Trifluridine and Tipiracil Tablets

2. Composition
Each film coated tablet contains:
Trifluridine I.P. .....15 mg
Tipiracil Hydrochloride 7.065 mg equivalent to Tipiracil 6.14 mg.
Colour: Titanium Dioxide I.P.
Each film coated tablet contains:
Trifluridine I.P. .....20 mg
Tipiracil Hydrochloride 9.420 mg equivalent to Tipiracil 8.19 mg.
Colours: Titanium Dioxide I.P. and Red Oxide of Iron.

3. Dosage form and strength
Film-coated tablet
15 mg Trifluridine and 6.14 mg Tipiracil
20 mg Trifluridine and 8.19 mg Tipiracil

4. Clinical particulars

4.1 Therapeutic indication

Metastatic Colorectal Cancer
Trifluridine and Tipiracil is indicated for the treatment of adult patients with metastatic colorectal cancer who have been 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.

4.2 Posology and method of administration
The recommended dosage of Trifluridine and Tipiracil is 35 mg/m² 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 Trifluridine and Tipiracil tablets 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.

Below Table 1 shows the calculated initial daily dose based on body surface area (BSA).

Table 1 - Starting dose calculation according to body surface area (BSA)

Starting dose	BSA (m²)	Dose in mg (2x daily)	Tablets per dose (2x daily)		Total daily dose (mg)
			15 mg/6.14 mg	20 mg/8.19 mg	
35 mg/m²	< 1.07	35	1	1	70
	1.07 - 1.22	40	0	2	80
	1.23 - 1.37	45	3	0	90
	1.38 - 1.52	50	2	1	100
	1.53 - 1.68	55	1	2	110
	1.69 - 1.83	60	0	3	120
	1.84 - 1.98	65	3	1	130
	1.99 - 2.14	70	2	2	140
	2.15 - 2.29	75	1	3	150
	≥ 2.30	80	0	4	160

Recommended dose adjustments
Dosing adjustments may be required based on individual safety and tolerability.
A maximum of 3 dose reductions is permitted to a minimum dose of 20 mg/m² twice daily. Dose escalation is not permitted after it has been reduced.
In the event of hematological and/or non-hematological toxicities patients should follow the dose interruption, resumption and reduction criteria stated in below Table 2, Table 3 and Table 4.

Table 2 - Dose interruption and resumption criteria for hematological toxicities related to myelosuppression

Parameter	Interruption criteria	Resumption criteria*
Neutrophils	< 0.5 × 10^9/L	≥ 1.5 × 10^9/L
Platelets	< 50 × 10^9/L	≥ 75 × 10^9/L

- Resumption criteria applied to the start of the next cycle for all patients regardless of whether or not the interruption criteria were met.

Table 3 - Recommended dose modifications for Trifluridine and Tipiracil in case of hematological and non-hematological adverse reactions

Adverse reaction	Recommended dose modifications
• Febrile neutropenia • CTCAE* Grade 4 neutropenia (< 0.5 x 10^9/L) or thrombocytopenia (< 25 × 10^9/L) that results in more than 1 week's delay in start of next cycle • CTCAE* non-hematologic Grade 3 or Grade 4 adverse reaction; except for Grade 3 nausea and/or vomiting controlled by antiemetic therapy or diarrhea responsive to antidiarrheal medicinal products	• Interrupt dosing until toxicity resolves to Grade 1 or baseline. • When resuming dosing, decrease the dose level by 5 mg/m²/dose from the previous dose level (Table 4). • Dose reductions are permitted to a minimum dose of 20 mg/m²/dose twice daily. • Do not increase dose after it has been reduced.

* Common terminology criteria for adverse events

Table 4 - Dose reductions according to body surface area (BSA)

Reduced dose	BSA (m²)	Dose in mg (2x daily)	Tablets per dose (2x daily)		Total daily dose (mg)
			15 mg/6.14 mg	20 mg/8.19 mg	
Level 1 dose reduction: From 35 mg/m² to 30 mg/m²					
30 mg/m²	< 1.09	30	2	0	60
	1.09 - 1.24	35	1	1	70
	1.25 - 1.39	40	0	2	80
	1.40 - 1.54	45	3	0	90
	1.55 - 1.69	50	2	1	100
	1.70 - 1.94	55	1	2	110
	1.95 - 2.09	60	0	3	120
	2.10 - 2.28	65	3	1	130
	≥ 2.29	70	2	2	140
Level 2 dose reduction: From 30 mg/m² to 25 mg/m²					
25 mg/m²	< 1.10	25*	2*	1*	50
	1.10 - 1.29	30	2	0	60
	1.30 - 1.49	35	1	1	70
	1.50 - 1.69	40	0	2	80
	1.70 - 1.89	45	3	0	90
	1.90 - 2.09	50	2	1	100
	2.10 - 2.29	55	1	2	110
	≥ 2.30	60	0	3	120
Level 3 dose reduction: From 25 mg/m² to 20 mg/m²					
20 mg/m²	< 1.14	20	0	1	40
	1.14 – 1.34	25*	2*	1*	50*
	1.35 – 1.59	30	2	0	60
	1.60 – 1.94	35	1	1	70
	1.95 – 2.09	40	0	2	80
	2.10 – 2.34	45	3	0	90
	≥ 2.35	50	2	1	100

*At a total daily dose of 50 mg, patients should take 1 x 20 mg/8.19 mg tablet in the morning and 2 x 15 mg/6.14 mg tablets in the evening.

4.3 Contraindications
None

4.4 Special warnings and precautions for use

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.

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/m² 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.

Gastrointestinal toxicity
Trifluridine and Tipiracil caused an increase in the incidence of gastrointestinal toxicities including nausea, vomiting and diarrhea. Patients with nausea, vomiting, diarrhea and other gastrointestinal toxicities should be carefully monitored and anti-emetic, anti-diarrheal and other measures, such as fluid/electrolyte replacement therapy, should be administered as clinically indicated. Dose modifications (delay and/or reduction) should be applied as necessary.

Proteinuria
Monitoring of proteinuria by dipstick urinalysis is recommended prior to starting and during therapy.

Lactose intolerance
Trifluridine and Tipiracil contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Drugs interactions
In vitro studies indicated that Trifluridine, Tipiracil, and 5-[trifluoromethyl] uracil (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.

4.6 Use in special populations

Pregnancy:
Based on animal data and its mechanism of action Trifluridine and Tipiracil can cause fetal harm. Trifluridine and Tipiracil caused embryo-fetal lethality and embryo-fetal toxicity in pregnant rats when given during gestation at doses resulting in exposures lower than or similar to human exposures at the recommended clinical dose. There are no available data on Trifluridine and Tipiracil use in pregnant women. Advise pregnant women of the potential risk to a fetus.

Renal impairment

Mild renal impairment (CrCl 60 to 89 mL/min) or **Moderate renal impairment** (CrCl 30 to 59 mL/min).
No adjustment of the starting dose is recommended in patients with mild or moderate renal impairment.

Severe renal impairment (CrCl 15 to 29 mL/min)
For patients with severe renal impairment a starting dose of 20 mg/m² twice daily is recommended. One dose reduction to a minimum dose of 15 mg/m² twice daily is permitted based on individual safety and tolerability (see Table 5). Dose escalation is not permitted after it has been reduced.

Table 5 - Starting dose and dose reduction in patients with severe renal impairment according to body surface area (BSA).

Reduced dose	BSA (m²)	Dose in mg (2x daily)	Tablets per dose (2x daily)		Total daily dose (mg)
			15 mg/6.14 mg	20 mg/8.19 mg	
Starting dose					
20 mg/m²	< 1.14	20	0	1	40
	1.14 – 1.34	25[a]	2[a]	1[a]	50[a]
	1.35 – 1.59	30	2	0	60
	1.60 – 1.94	35	1	1	70
	1.95 – 2.09	40	0	2	80
	2.10 – 2.34	45	3	0	90
	≥ 2.35	50	2	1	100
Dose reduction: From 20 mg/m² to 15 mg/m²					
15 mg/m²	< 1.15	15	1	0	30
	1.15 – 1.49	20	0	1	40
	1.50 – 1.84	25[a]	2[a]	1[a]	50[a]
	1.85 – 2.09	30	2	0	60
	2.10 – 2.34	35	1	1	70
	≥ 2.35	40	0	2	80

[a] At a total daily dose of 50 mg, patients should take 1 x 20 mg/8.19 mg tablet in the morning and 2 x 15 mg/6.14 mg tablets in the evening.

End stage renal disease (CrCl below 15 mL/min or requiring dialysis)
Administration is not recommended in patients with end stage renal disease as there are no data available for these patients.

Hepatic impairment

Mild hepatic impairment
No adjustment of the starting dose is recommended in patients with mild hepatic impairment.

Moderate or severe hepatic impairment
Administration is not recommended in patients with baseline moderate or severe hepatic impairment (National Cancer Institute [NCI] Criteria Group C and D defined by total bilirubin > 1.5 x ULN) as, a higher incidence of Grade 3 or 4 hyperbilirubinemia is observed in patients with baseline moderate hepatic impairment, although this is based on very limited data.
Animal Data
Trifluridine/Tipiracil was administered orally once daily to female rats during organogenesis at dose levels of 15, 50 and 150 mg/kg [Trifluridine (FTD) equivalent]. Decreased fetal weight was observed at FTD doses ≥50 mg/kg (approximately 0.33 times the FTD exposure at the clinical dose of 35 mg/m² twice daily). At the FTD dose of 150 mg/kg (approximately 0.92 times the FTD exposure at the clinical dose of 35 mg/m² twice daily) embryo lethality and structural anomalies (kinked tail, cleft palate, ectrodactyly, anasarca, alterations in great vessels and skeletal anomalies) were observed.

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. In nursing rats, Trifluridine and Tipiracil or their metabolites were present in breast milk *(see Data)*. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with Trifluridine and Tipiracil and for 1 day following the final dose.

Data
Radioactivity was excreted in the milk of nursing rats dosed with Trifluridine/Tipiracil containing ^{14}C-FTD or ^{14}C-Tipiracil (TPI). Levels of FTD-derived radioactivity were as high as approximately 50% of the exposure in maternal plasma an hour after dosing with Trifluridine/Tipiracil and were approximately the same as those in maternal plasma for up to 12 hours following dosing. Exposure to TPI-derived radioactivity was higher in milk than in maternal plasma beginning 2 hours after dosing and continuing for at least 12 hours following administration of Trifluridine/Tipiracil.

Pediatric Use
Safety and effectiveness of Trifluridine and Tipiracil in pediatric patients have not been established.
Animal Toxicity Data
Dental toxicity including whitening, breakage and malocclusion (degeneration and disarrangement in the ameloblasts, papillary layer cells and odontoblasts) were observed in rats treated with Trifluridine/Tipiracil at doses ≥ 50 mg/kg (approximately 0.33 times the exposure at the clinical dose of 35 mg/m² twice daily).

Geriatric Use
In RECOURSE and TAGS, 868 patients received Trifluridine and Tipiracil; 45% were 65 years of age or over, while 10% were 75 and over. No overall differences in effectiveness were observed in patients 65 or older versus younger patients. Patients 65 years of age or older who received Trifluridine and Tipiracil had a higher incidence of the following hematologic laboratory abnormalities compared to patients younger than 65 years: Grade 3 or 4 neutropenia (46% vs. 32%), Grade 3 anemia (22% vs. 16%) and Grade 3 or 4 thrombocytopenia (7% vs. 4%).

4.7 Effects on ability to drive and use machines
Trifluridine and Tipiracil has minor influence on the ability to drive and use machines. Fatigue, dizziness or malaise may occur during treatment.

4.8 Undesirable effects
The Trifluridine and Tipiracil was evaluated in RECOURSE, a randomized (2:1), double-blind, placebo-controlled trial in patients

with previously treated metastatic colorectal cancer. Patients received Trifluridine and Tipiracil 35 mg/m²/dose (n=533) or placebo (n=265) twice daily on Days 1 through 5 and Days 8 through 12 of each 28-day cycle. In RECOURSE, 12% of patients received Trifluridine and Tipiracil for more than 6 months and 1% of patients received Trifluridine and Tipiracil more than 1 year.

The study population characteristics were: median age 63 years; 61% male; 57% White, 35% Asian and 1% Black. The most common adverse reactions or laboratory abnormalities (≥10% in incidence) in patients treated with Trifluridine and Tipiracil at a rate that exceeds the rate in patients receiving placebo were anemia, neutropenia, asthenia/fatigue, nausea, thrombocytopenia, decreased appetite, diarrhea, vomiting, abdominal pain and pyrexia.

In RECOURSE, 3.6% of patients discontinued Trifluridine and Tipiracil for an adverse reaction and 14% of patients required a dose reduction. The most common adverse reactions or laboratory abnormalities leading to dose reduction were neutropenia, anemia, febrile neutropenia, fatigue and diarrhea.

Table 6 - Adverse Reactions (≥5%) in Patients Receiving Trifluridine and Tipiracil and at a Higher Incidence (>2%) than in Patients Receiving Placebo in RECOURSE

Adverse Reactions	Trifluridine/Tipiracil (N=533)		Placebo (N=265)	
	All Grades (%)	Grades 3-4* (%)	All Grades (%)	Grades 3-4* (%)
General				
Asthenia/fatigue	52	7	35	9
Pyrexia	19	1	14	<1
Gastrointestinal				
Nausea	48	2	24	1
Diarrhea	32	3	12	<1
Vomiting	28	2	14	<1
Abdominal pain	21	2	18	4
Stomatitis	8	<1	6	0
Metabolism and nutrition				
Decreased appetite	39	4	29	5
Infections†	27	6	16	5
Nervous system				
Dysgeusia	7	0	2	0
Skin and subcutaneous tissue				
Alopecia	7	0	1	0

Laboratory Abnormalities in RECOURSE

Laboratory Parameters*	Trifluridine/Tipiracil		Placebo	
	All Grades (%)	Grades 3-4* (%)	All Grades (%)	Grades 3-4* (%)
Hematologic				
Anemia†	77	18	33	3
Neutropenia	67	38	1	0
Thrombocytopenia	42	5	8	<1

* Worst Grade at least one grade higher than baseline, with percentages based on number of patients with post baseline samples, which may be <533 (Trifluridine and Tipiracil) or 265 (placebo).
† One Grade 4 anemia adverse reaction based on clinical criteria was reported.

4.9 Overdose

The highest dose of Trifluridine and Tipiracil administered in clinical trials was 180 mg/m² per day. The adverse drug reactions reported in association with overdoses were consistent with the established safety profile. The primary anticipated complication of an overdose is bone marrow suppression. There is no known antidote for an overdose of Trifluridine and Tipiracil. Medical management of an overdose should include customary therapeutic and supportive medical intervention aimed at correcting the presenting clinical manifestations and preventing their possible complications.

5. Pharmacological properties

Pharmacotherapeutic group: antineoplastic agents, antimetabolites.

5.1 Mechanism of Action

Trifluridine and Tipiracil is comprised of an antineoplastic thymidine-based nucleoside analogue, Trifluridine and the thymidine phosphorylase (TPase) inhibitor, Tipiracil hydrochloride, at a molar ratio 1:0.5. Following uptake into cancer cells, Trifluridine, is phosphorylated by thymidine kinase, further metabolised in cells to a deoxyribonucleic acid DNA substrate, and incorporated directly into DNA, thereby interfering with DNA function to prevent cell proliferation.

However, Trifluridine is rapidly degraded by TPase and readily metabolised by a first-pass effect following oral administration, hence the inclusion of the TPase inhibitor, Tipiracil hydrochloride.

In nonclinical studies, Trifluridine/Tipiracil hydrochloride demonstrated antitumour activity against both 5-fluorouracil (5-FU) sensitive and resistant colorectal cancer cell lines. The cytotoxic activity of Trifluridine/Tipiracil hydrochloride against several human tumour xenografts correlated highly with the amount of Trifluridine incorporated into DNA, suggesting this as the primary mechanism of action.

5.2 Pharmacodynamic properties

Trifluridine and Tipiracil had no clinically relevant effect on QT/QTc prolongation compared with placebo in an open label study in patients with advanced solid tumours.

5.3 Pharmacokinetic properties

Absorption

After oral administration of Trifluridine and Tipiracil with [^{14}C]-Trifluridine, at least 57% of the administered Trifluridine was absorbed and only 3% of the dose was excreted into feces. After oral administration of Trifluridine and Tipiracil with [^{14}C]-Tipiracil hydrochloride, at least 27% of the administered Tipiracil hydrochloride was absorbed and 50% of the total radioactivity dose measured into feces, suggestive of moderate gastrointestinal absorption of Tipiracil hydrochloride.

Following a single dose of Trifluridine and Tipiracil (35 mg/m²) in patients with advanced solid tumours, the mean times to peak plasma concentrations (T_{max}) of Trifluridine and Tipiracil hydrochloride were around 2 hours and 3 hours, respectively.

In the pharmacokinetic (PK) analyses of the multiple dose administration of Trifluridine and Tipiracil (35 mg/m²/dose, twice daily for 5 days a week with 2 days rest for 2 weeks followed by a 14-day rest, repeated every 4 weeks), Trifluridine area under the concentration-time curve from time 0 to the last measurable concentration ($AUC_{0\text{-last}}$) was approximately 3-fold higher and maximum concentration (C_{max}) was approximately 2-fold higher after multiple dose administration (Day 12 of Cycle 1) of Trifluridine and Tipiracil than after single-dose (Day 1 of Cycle 1).

However, there was no accumulation for Tipiracil hydrochloride, and no further accumulation of Trifluridine with successive cycles (Day 12 of Cycles 2 and 3) of administration of Trifluridine and Tipiracil. Following multiple doses of Trifluridine and Tipiracil (35 mg/m²/dose twice daily) in patients with advanced solid tumours, the mean times to peak plasma concentrations (T_{max}) of Trifluridine and Tipiracil hydrochloride were around 2 hours and 3 hours, respectively.

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/m².

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%.

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 [^{14}C]-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 [^{14}C]-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.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Repeat-dose toxicity

Toxicology assessment of Trifluridine/Tipiracil hydrochloride was performed in rats, dogs and monkeys. The target organs identified were the lymphatic and hematopoietic systems and the gastrointestinal tract. All changes, i.e., leukopenia, anemia, bone marrow hypoplasia, atrophic changes in the lymphatic and hematopoietic tissues and the gastrointestinal tract, were reversible within 9 weeks of drug withdrawal. Whitening, breakage, and malocclusion were observed in teeth of rats treated with Trifluridine/Tipiracil hydrochloride, which are considered rodent specific and not relevant for human.

Carcinogenesis and mutagenesis

No long term studies evaluating the carcinogenic potential of Trifluridine/Tipiracil hydrochloride in animals have been performed. Trifluridine was shown to be genotoxic in a reverse mutation test in bacteria, a chromosomal aberration test in mammal-cultured cells, and a micronucleus test in mice. Therefore, Trifluridine and Tipiracil should be treated as a potential carcinogen.

Reproductive toxicity

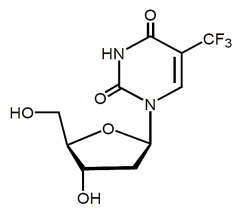
Results of animal studies did not indicate an effect of Trifluridine and Tipiracil hydrochloride on male and female fertility in rats. The increases in the corpus luteum count and implanting embryo count observed in female rats at high doses were not considered adverse (see section 4.6). Trifluridine and Tipiracil has been shown to cause embryo-fetal lethality and embryo-fetal toxicity in pregnant rats when given at dose levels lower than the clinical exposure. No peri/post-natal developmental toxicity studies have been performed.

7. Description

TIPANAT contains Trifluridine and Tipiracil hydrochloride at a molar ratio of 1:0.5.

Trifluridine

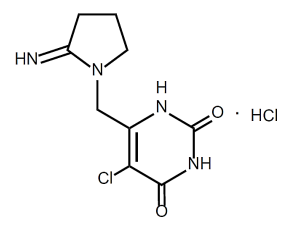
Trifluridine, a nucleoside metabolic inhibitor, is described chemically as 2'-deoxy-5-(trifluoromethyl) uridine and has the following structural formula:



Trifluridine is a white crystalline powder, soluble in water, ethanol, 0.01 mol/L hydrochloric acid, 0.01 mol/L sodium hydroxide solution; freely soluble in methanol, acetone; sparingly soluble in 2- propanol, acetonitrile; slightly soluble in diethyl ether; and very slightly soluble in isopropyl ether.

Tipiracil hydrochloride

Tipiracil hydrochloride, a thymidine phosphorylase inhibitor, is described chemically as 5chloro-6-[(2-iminopyrrolidin-1-yl)methyl] pyrimidine-2,4-(1H,3H)-dione monohydrochloride or 2,4(1H,3H)-Pyrimidinedione, 5-chloro-6-[(2-imino-1-pyrrolidinyl)methyl]-, hydrochloride (1:1), and has the following structural formula:



Tipiracil hydrochloride is a white crystalline powder, soluble in water, 0.01 mol/L hydrochloric acid, and 0.01 mol/L sodium hydroxide; slightly soluble in methanol; very slightly soluble in ethanol; and practically insoluble in acetonitrile, 2-propanol, acetone, diisopropyl ether, and diethyl ether.

TIPANAT tablets for oral use.

8. Pharmaceutical particulars

8.1 Incompatibilities

Not applicable.

8.2 Shelf-life

24 Months

8.3 Packaging information

Tipanat 15 - Bottle pack of 20 tablets with prescribing information housed in a carton.
Tipanat 20 - Bottle pack of 20 tablets with prescribing information housed in a carton.

8.4 Storage and handing instructions

Store below 30°C.

9. Patient Counselling Information

Severe Myelosuppression

Advise patients to immediately contact their healthcare provider if they experience signs or symptoms of infection and advise patients to keep all appointments for blood tests.

Gastrointestinal Toxicity

- Advise patients to contact their healthcare provider for severe or persistent nausea, vomiting, diarrhea or abdominal pain.

Administration Instructions

- Advise patients that Trifluridine and Tipiracil is available in two strengths and they may receive both strength tablets to provide the prescribed dosage.
- Advise patients to take Trifluridine and Tipiracil with food.
- Advise patients that anyone else who handles their medication should wear gloves.

Embryo-Fetal Toxicity

- Advise pregnant women and females of reproductive potential of the potential risk to the fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy.

Lactation

- Advise women not to breastfeed during treatment with Trifluridine and Tipiracil and for 1 day following the final dose.

10. Date of revision

September 2021

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NATCO PHARMA LIMITED,
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References:

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2. https://www.ema.europa.eu/en/documents/product-information/lonsurf-epar-product-information_en.pdf