SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Trifluridine/Tipiracil Servier 20 mg/8.19 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Trifluridine/ Tipiracil 20 mg/8.19 mg film-coated tablets

Each film-coated tablet contains 20 mg trifluridine and 8.19 mg tipiracil (as hydrochloride).

Excipient with known effect

Each film-coated tablet contains 120.980 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Trifluridine/ Tipiracil 15 mg/6.14 mg film-coated tablets
The tablet is a white, biconvex, round, film-coated tablet, with a diameter of 7.1 mm and a thickness of 2.7 mm, imprinted with ‘15’ on one side, and ‘102’ and ’15 mg’ on the other side, in grey ink.

Trifluridine/ Tipiracil 20 mg/8.19 mg film-coated tablets
The tablet is a pale red, biconvex, round, film-coated tablet, with a diameter of 7.6 mm and a thickness of 3.2 mm, imprinted with ‘20’ on one side, and ‘102’ and ‘20 mg’ on the other side, in grey ink.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Colorectal cancer

Trifluridine/ Tipiracil is indicated in combination with bevacizumab for the treatment of adult patients with metastatic colorectal cancer (CRC) who have received two prior anticancer treatment regimens including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and/or anti- EGFR agents.

Trifluridine/ Tipiracil is indicated as monotherapy for the treatment of adult patients with metastatic colorectal cancer who have been previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents.

Gastric cancer

Trifluridine/ Tipiracil is indicated as monotherapy for the treatment of adult patients with metastatic gastric cancer including adenocarcinoma of the gastroesophageal junction, who have been previously treated with at least two prior systemic treatment regimens for advanced disease (see section 5.1).

4.2 Posology and method of administration

Trifluridine/ Tipiracil should be prescribed by physicians experienced in the administration of anticancer therapy.

Posology

The recommended starting dose of Trifluridine/ Tipiracil in adults, as monotherapy or in combination with bevacizumab, is 35 mg/m^2/dose administered orally twice daily on Days 1 to 5 and Days 8 to 12 of each 28-day cycle until disease progression or unacceptable toxicity (see section 4.4).

When Trifluridine/ Tipiracil is used in combination with bevacizumab for the treatment of metastatic CRC, the dose of bevacizumab is 5 mg/kg of body weight given once every 2 weeks. Please refer to the full product information for bevacizumab.

The dose is calculated according to body surface area (BSA) (see Table 1). The dose must not exceed 80 mg/dose.

If doses were missed or held, the patient must not make up for missed doses.

Table 1 - Starting dose calculation according to BSA

Starting dose	BSA (m^2)	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/m^2	< 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 are permitted to a minimum dose of 20 mg/m^2 twice daily. Dose escalation is not permitted after it has been reduced.

In the event of haematological and/or non-haematological toxicities patients should follow the dose interruption, resumption and reduction criteria stated in Table 2, Table 3 and Table 4.

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

Parameter	Interruption criteria	Resumption criteria[a]
Neutrophils	< 0.5 □ 10^9/L	□ 1.5 □ 10^9/L
Platelets	< 50 □ 10^9/L	□ 75 □ 10^9/L

[a] Resumption criterion 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/ Tipiracilin case of haematological and non-haematological 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-haematologic Grade 3 or Grade 4 adverse reaction; except for Grade 3 nausea and/or vomiting controlled by antiemetic therapy or diarrhoea responsive to antidiarrhoeal medicinal products	• Interrupt dosing until toxicity resolves to Grade 1 or baseline. • When resuming dosing, decrease the dose level by 5 mg/m^2/dose from the previous dose level (Table 4). • Dose reductions are permitted to a minimum dose of 20 mg/m^2/dose twice daily (or 15 mg/m^2/dose twice daily in severe renal impairment). • Do not increase dose after it has been reduced.

* Common terminology criteria for adverse events

Table 4 - Dose reductions according to BSA

Reduced dose	BSA (m^2)	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/m^2 to 30 mg/m^2					
30 mg/m^2	< 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/m^2 to 25 mg/m^2					
25 mg/m^2	< 1.10	25[a]	2[a]	1[a]	50[a]
	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/m^2 to 20 mg/m^2					
20 mg/m^2	< 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

[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.

Special populations

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 (see sections 4.4 and 5.2).

- *Severe renal impairment (CrCl 15 to 29 mL/min)*

For patients with severe renal impairment a starting dose of 20 mg/m^2 twice daily is recommended (see sections 4.4 and 5.2). One dose reduction to a minimum dose of 15 mg/m^2 twice daily is permitted

based on individual safety and tolerability (see Table 5). Dose escalation is not permitted after it has been reduced.

In the event of haematological and/or non-haematological toxicities patients should follow the dose interruption, resumption and reduction criteria stated in Table 2, Table 3 and Table 5.

Table 5 – Starting dose and dose reduction in patients with severe renal impairment according to BSA

Reduced dose	**BSA (m^2)**	**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/m^2	< 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/m^2 to 15 mg/m^2					
15 mg/m^2	< 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 (see section 4.4).

Hepatic impairment

- *Mild hepatic impairment*

No adjustment of the starting dose is recommended in patients with mild hepatic impairment (see section 5.2).

- *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 hyperbilirubinaemia is observed in patients with baseline moderate hepatic impairment, although this is based on very limited data (see sections 4.4 and 5.2).

Elderly

No adjustment of the starting dose is required in patients ≥ 65 years old (see sections 4.8, 5.1 and 5.2). Efficacy and safety data in patients over 75 years old is limited.

Paediatric population

There is no relevant use of trifluridine/ tipiracil in the paediatric population for the indications of metastatic colorectal cancer and metastatic gastric cancer.

Race

No adjustment of the starting dose is required on the basis of patient's race (see

sections 5.1 and 5.2). There is limited data on trifluridine/ tipiracil in Black/African American patients but there is no biological rationale to expect any difference between this subgroup and the overall population.

Method of administration

Trifluridine/ Tipiracil is for oral use. The tablets must be taken with a glass of water within 1 hour after completion of the morning and evening meals.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Bone marrow suppression

Trifluridine/ Tipiracil caused an increase in the incidence of myelosuppression including anaemia, neutropenia, leukopenia, and thrombocytopenia.

Complete blood cell counts must be obtained prior to initiation of therapy and as needed to monitor toxicity, but at a minimum, prior to each treatment cycle.

Treatment must not be started if the absolute neutrophil count is < 1.5 □ 10^9/L, if the platelet counts are
< 75 □ 10^9/L, or if the patient has an unresolved Grade 3 or 4 non-haematological clinically relevant toxicity from prior therapies.

Serious infections have been reported following treatment with trifluridine/ tipiracil (see section 4.8). Given that the majority were reported in the context of bone marrow suppression, the patient's condition should be monitored closely, and appropriate measures, such as antimicrobial agents and granulocyte-colony stimulating factor (G-CSF), should be administered as clinically indicated. In RECOURSE, TAGS and SUNLIGHT studies, 9.4%, 17.3% and 19.5% of patients in the trifluridine/ tipiracil group respectively received G-CSF mainly for therapeutic use. In the SUNLIGHT study, 29.3% of patients in the trifluridine/ tipiracil with bevacizumab group received G-CSF including 16.3% for therapeutic use.

Gastrointestinal toxicity

Trifluridine/ Tipiracil caused an increase in the incidence of gastrointestinal toxicities including nausea, vomiting and diarrhoea.

Patients with nausea, vomiting, diarrhoea and other gastrointestinal toxicities should be carefully monitored, and anti-emetic, anti-diarrhoeal 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 (see section 4.2).

Renal impairment

Trifluridine/ Tipiracil is not recommended for use in patients with end-stage renal disease (creatinine clearance [CrCl] < 15 mL/min or requiring dialysis), as trifluridine/ tipiracil has not been studied in these patients (see section 5.2).

The global incidence of adverse events (AEs) is similar in normal renal function (CrCl ≥ 90 mL/min), mild (CrCl = 60 to 89 mL/min) or moderate (CrCl = 30 to 59 mL/min) renal impairment subgroups. However, the incidence of serious, severe AEs and AEs leading to dose modification tends to increase with advancing levels of renal impairment. In addition, a higher exposure of trifluridine and tipiracil hydrochloride was observed in patients with moderate renal impairment, compared with patients with normal renal function or patients with mild renal impairment (see section 5.2).

Patients with severe renal impairment (CrCl = 15 to 29 mL/min) and adjusted starting dose of

20 mg/m2 twice daily had a safety profile consistent with the safety profile of trifluridine/ tipiracil in patients with normal renal function or mild renal impairment. Their exposure to trifluridine was similar to that of patients with normal renal function and their exposure to tipiracil hydrochloride was increased compared to patients with normal renal function, mild and moderate renal impairment (see sections 4.2 and 5.2).

Patients with renal impairment should be monitored closely when being treated with trifluridine/ tipiracil; patients with moderate or severe renal impairment should be more frequently monitored for haematological toxicities.

Hepatic impairment

Trifluridine/ Tipiracil is not recommended for use 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 hyperbilirubinaemia is observed in patients with baseline moderate hepatic impairment, although this is based on very limited data (see section 5.2).

Proteinuria

Monitoring of proteinuria by dipstick urinalysis is recommended prior to starting and during therapy (see section 4.8).

Lactose intolerance

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

4.5 Interaction with other medicinal products and other forms of interaction

In vitro studies indicated that trifluridine, tipiracil hydrochloride and 5-[trifluoromethyl] uracil (FTY) did not inhibit the activity of human cytochrome P450 (CYP) isoforms. In vitro evaluation indicated that trifluridine, tipiracil hydrochloride and FTY had no inductive effect on human CYP isoforms (see section 5.2).

In vitro studies indicated that trifluridine is a substrate for the nucleoside transporters CNT1, ENT1 and ENT2. Therefore, caution is required when using medicinal products that interact with these transporters. Tipiracil hydrochloride was a substrate for OCT2 and MATE1, therefore, the concentration might be increased when trifluridine/ tipiracil is administered concomitantly with inhibitors of OCT2 or MATE1.

Caution is required when using medicinal products that are human thymidine kinase substrates, e.g., zidovudine. Such medicinal products, if used concomitantly with trifluridine/ tipiracil, may compete with the effector, trifluridine, for activation via thymidine kinases. Therefore, when using antiviral medicinal products that are human thymidine kinase substrates, monitor for possible decreased efficacy of the antiviral medicinal product, and consider switching to an alternative antiviral medicinal product that is not a human thymidine kinase substrate, such as lamivudine, didanosine and abacavir (see section 5.1).

It is unknown whether trifluridine/ tipiracil may reduce the effectiveness of hormonal contraceptives. Therefore, women using hormonal contraceptive must also use a barrier contraceptive method.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

Based on findings in animals, trifluridine may cause foetal harm when administered to pregnant women. Women should avoid becoming pregnant while taking trifluridine/ tipiracil and for up to 6 months after ending treatment. Therefore, women of child-bearing potential must use highly effective contraceptive measures while taking trifluridine/ tipiracil and for 6 months after stopping treatment. It is currently unknown whether trifluridine/ tipiracil may reduce the effectiveness of hormonal contraceptives, and therefore women using hormonal contraceptives should add a barrier contraceptive method.
Men with a partner of child-bearing potential must use effective contraception during treatment and for up to 6 months after discontinuation of treatment.

Pregnancy

There are no available data from the use of trifluridine/ tipiracil in pregnant women. Based on the mechanism of action, trifluridine is suspected to cause congenital malformations when administered during pregnancy. Studies in animals have shown reproductive toxicity (see section 5.3). Trifluridine/ Tipiracil should not be used during pregnancy unless the clinical condition of the woman requires treatment with trifluridine/ tipiracil.

Breast-feeding

It is unknown whether trifluridine/ tipiracil or its metabolites are excreted in human milk. Studies in animals have shown excretion of trifluridine, tipiracil

hydrochloride and/or their metabolites in milk (see section 5.3). A risk to the suckling child cannot be excluded. Breast-feeding should be discontinued during treatment with trifluridine/ tipiracil.

Fertility

There are no data available on the effects of trifluridine/ tipiracil on human fertility. Results of animal studies did not indicate an effect of trifluridine/ tipiracil on male or female fertility (see section 5.3). Patients who wish to conceive a child should be advised to seek reproductive counselling and cryo-conservation of either the ovum or sperm prior to starting trifluridine/ tipiracil treatment.

4.7 Effects on ability to drive and use machines

Trifluridine/ Tipiracil has minor influence on the ability to drive and use machines. Fatigue, dizziness or malaise may occur during treatment (see section 4.8).

4.8 Undesirable effects

Summary of safety profile

The most serious observed adverse reactions in patients receiving trifluridine/ tipiracil are bone marrow suppression and gastrointestinal toxicity (see section 4.4).

Trifluridine/ Tipiracil as monotherapy

The safety profile of trifluridine/ tipiracil as monotherapy is based on the pooled data from 1114 patients with metastatic colorectal or gastric cancer in controlled phase III clinical studies.

The most common adverse reactions (≥ 30%) are neutropenia (53% [34% ≥ Grade 3]), nausea (31 % [1% ≥ Grade 3]), fatigue (31% [4% ≥ Grade 3]), and anaemia (30 % [11% ≥ Grade 3]). The most common adverse reactions (≥ 2%) that resulted in treatment discontinuation, dose reduction, dose delay, or dose interruption were neutropenia, anaemia, fatigue, leukopenia, thrombocytopenia, diarrhoea, and nausea.

Trifluridine/ Tipiracil in combination with bevacizumab

The safety profile of trifluridine/ tipiracil in combination with bevacizumab is based on the data from 246 patients with metastatic colorectal cancer in the controlled phase III clinical study (SUNLIGHT).
The most common adverse reactions (≥ 30%) are neutropenia (69% [48% ≥ Grade 3]), fatigue (35% [3%
≥ Grade 3]), and nausea (33% [1% ≥ Grade 3]).

The most common adverse reactions (≥ 2%) that resulted in treatment discontinuation, dose reduction, dose delay, or dose interruption of trifluridine/ tipiracil when used in combination with bevacizumab were neutropenia, fatigue, thrombocytopenia, nausea and anaemia.

When trifluridine/ tipiracil is used in combination with bevacizumab, the frequency of the following adverse reactions was increased compared to trifluridine/ tipiracil as monotherapy: neutropenia (69% vs 53%), severe neutropenia (48% vs 34%), thrombocytopenia (24% vs 16%), stomatitis (11% vs 6%).

The adverse reactions observed from the 533 treated patients with metastatic colorectal cancer in the placebo-controlled Phase III (RECOURSE) clinical study, the 335 treated patients with metastatic gastric cancer in the placebo-controlled Phase III (TAGS) clinical study, the 246 patients treated with trifluridine/ tipiracil in monotherapy and the 246 patients treated with trifluridine/ tipiracil in combination with bevacizumab for metastatic colorectal cancer in the controlled Phase III (SUNLIGHT) clinical study are shown in Table 6. They are classified according to System Organ Class (SOC) and the appropriate Medical Dictionary for Regulatory (MedDRA) term is used to describe a certain drug reaction and its synonyms and related conditions.

Adverse reactions known to occur with trifluridine/ tipiracil given alone or with bevacizumab may occur during treatment with these medicinal products in combination, even if these reactions were not reported in clinical trials with combination therapy.

Adverse reactions are grouped according to their frequencies. Frequency groups are defined by the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥1/1,000 to < 1/100); and rare (≥ 1/10 000 to < 1/1 000).

Within each frequency group, adverse drug reactions are presented in order of decreasing seriousness.

Table 6 – Adverse reactions reported in clinical studies in patients treated with Trifluridine/ Tipiracil

System Organ Class (MedDRA)[a]	**Adverse reactions**	**Frequency**	
		Monotherapy	**Combination with bevacizumab**
Infections and infestations	Lower respiratory tract infection	Common	-
	Neutropenic sepsis	Uncommon	-
	Biliary tract infection	Uncommon	-
	Infection	Uncommon	Common
	Urinary tract infection	Uncommon	Uncommon
	Bacterial infection	Uncommon	-
	Candida infection	Uncommon	-
	Conjunctivitis	Uncommon	-
	Herpes zoster	Uncommon	-
	Influenza	Uncommon	-
	Upper respiratory tract infection	Uncommon	-
	Enteritis infectious	Rare	-
	Septic shock[b]	Rare	-
	Gingivitis	Rare	Uncommon
	Tinea pedis	Rare	-
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Cancer pain	Uncommon	-
Blood and lymphatic system disorders	Anaemia	Very common	Very common
	Neutropenia	Very common	Very common

	Leukopenia	Very common	Common
	Thrombocytopenia	Very common	Very common
	Febrile neutropenia	Common	Uncommon
	Lymphopenia	Common	Common
	Pancytopenia	Uncommon	Uncommon
	Erythropenia	Uncommon	-
	Leukocytosis	Uncommon	-
	Monocytopenia	Uncommon	-
	Monocytosis	Uncommon	-
	Granulocytopenia	Rare	-
Metabolism and nutrition disorders	Hypoalbuminaemia	Very common	Very common
	Dehydration	Common	Uncommon
	Hyperglycaemia	Uncommon	-
	Hyperkalaemia	Uncommon	Uncommon
	Hypocalcaemia	Uncommon	-
	Hypokalaemia	Uncommon	-
	Hyponatraemia	Uncommon	-
	Hypophosphataemia	Uncommon	-
	Gout	Uncommon	-
	Hypernatraemia	Rare	-
Psychiatric disorders	Anxiety	Uncommon	-
	Insomnia	Uncommon	-
Nervous system disorders	Dysgeusia	Common	Common
	Dizziness	Uncommon	Common
	Headache	Uncommon	Common
	Neuropathy peripheral	Uncommon	Uncommon
	Paraesthesia	Uncommon	Uncommon
	Lethargy	Uncommon	-
	Neurotoxicity	Uncommon	-
	Burning sensation	Rare	-
	Dysaesthesia	Rare	-
	Hyperaesthesia	Rare	-
	Hypoaesthesia	Rare	-
	Syncope	Rare	-
Eye disorders	Cataract	Rare	-
	Diplopia	Rare	-
	Dry eye	Rare	-
	Vision blurred	Rare	-
	Visual acuity reduced	Rare	-
Ear and labyrinth disorders	Vertigo	Uncommon	-
	Ear discomfort	Rare	-
Cardiac disorders	Angina pectoris	Uncommon	-
	Arrhythmia	Uncommon	-
	Palpitations	Uncommon	-
Vascular disorders	Hypertension	Uncommon	Common
	Flushing	Uncommon	-
	Hypotension	Uncommon	-
	Embolism	Rare	-
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Common	Common
	Pulmonary embolism[b]	Uncommon	-
	Dysphonia	Uncommon	Uncommon
	Cough	Uncommon	-

	Epistaxis	Uncommon	-
	Rhinorrhoea	Rare	Uncommon
	Oropharyngeal pain	Rare	-
	Pleural effusion	Rare	-
Gastrointestinal disorders	Diarrhoea	Very common	Very common
	Vomiting	Very common	Very common
	Nausea	Very common	Very common
	Abdominal pain	Common	Common
	Stomatitis	Common	Very common
	Constipation	Common	Common
	Ileus	Uncommon	-
	Gastrointestinal haemorrhage	Uncommon	-

	Colitis	Uncommon	Uncommon
	Mouth ulceration	Uncommon	Common
	Oral disorder	Uncommon	Common
	Abdominal distension	Uncommon	Uncommon
	Anal inflammation	Uncommon	Uncommon
	Dyspepsia	Uncommon	Uncommon
	Flatulence	Uncommon	Uncommon
	Gastritis	Uncommon	-
	Gastrooesophageal reflux disease	Uncommon	-
	Glossitis	Uncommon	-
	Impaired gastric emptying	Uncommon	-
	Retching	Uncommon	-
	Tooth disorder	Uncommon	-
	Ascites	Rare	-
	Pancreatitis acute	Rare	-
	Subileus	Rare	-
	Breath odour	Rare	-
	Buccal polyp	Rare	-
	Enterocolitis haemorrhagic	Rare	-
	Gingival bleeding	Rare	-
	Oesophagitis	Rare	-
	Periodontal disease	Rare	-
	Proctalgia	Rare	-
	Reflux gastritis	Rare	-
Hepatobiliary disorders	Hyperbilirubinaemia	Common	Common
	Hepatotoxicity	Uncommon	-
	Biliary dilatation	Rare	-
Skin and subcutaneous tissue disorders	Alopecia	Common	Common
	Dry skin	Common	Common
	Pruritus	Common	Uncommon
	Rash	Common	Uncommon
	Nail disorder	Uncommon	Uncommon
	Palmar-plantar erythrodysaesthesia syndrome[c]	Uncommon	Uncommon
	Acne	Uncommon	-
	Hyperhidrosis	Uncommon	-
	Urticaria	Uncommon	-
	Blister	Rare	-
	Erythema	Rare	-
	Photosensitivity reaction	Rare	-
	Skin exfoliation	Rare	-
Musculoskeletal and connective tissue disorders	Arthralgia	Uncommon	Common
	Myalgia	Uncommon	Common
	Muscular weakness	Uncommon	Uncommon
	Pain in extremity	Uncommon	Uncommon
	Bone pain	Uncommon	-
	Limb discomfort	Uncommon	-
	Muscle spasms	Uncommon	-
	Joint swelling	Rare	-

Renal and urinary disorders	Proteinuria	Common	Uncommon
	Renal failure	Uncommon	-
	Haematuria	Uncommon	-
	Micturition disorder	Uncommon	-
	Cystitis noninfective	Rare	-
	Leukocyturia	Rare	-
Reproductive system and breast disorders	Menstrual disorder	Rare	Uncommon
General disorders and administration site conditions	Fatigue	Very common	Very common
	Pyrexia	Common	Uncommon
	Mucosal inflammation	Common	Uncommon
	Malaise	Common	-
	Oedema	Common	-
	General physical health deterioration	Uncommon	-
	Pain	Uncommon	Uncommon
	Feeling of body temperature change	Uncommon	-
	Xerosis	Rare	-
Investigations	Weight decreased	Common	Common
	Hepatic enzyme increased	Common	Common
	Blood alkaline phosphatase increased	Common	Uncommon
	Blood lactate dehydrogenase increased	Uncommon	-
	C-reactive protein increased	Uncommon	-
	Blood creatinine increased	Uncommon	-
	Blood urea increased	Uncommon	-
	Haematocrit decreased	Uncommon	-
	International normalised ratio increased	Uncommon	-
	Activated partial thromboplastin time prolonged	Rare	-
	Electrocardiogram QT prolonged	Rare	-
	Protein total decreased	Rare	-

a. Different MedDRA preferred terms that were considered clinically similar have been grouped into a single term.
b. Fatal cases have been reported.
c. Hand-foot skin reaction.

Elderly

Patients 65 years of age or older who received trifluridine/ tipiracil as monotherapy had a higher incidence (≥5%) of the following treatment-related adverse events compared to patients younger than 65 years: neutropenia (58.9% vs 48.2%), severe neutropenia (41.3% vs 27.9%), anaemia (36.5% vs 25.2%), severe anaemia (14.1% vs 8.9%), decreased appetite (22.6% vs 17.4%), and thrombocytopenia (21.4% vs 12.1%). When trifluridine/ tipiracil is used in combination with bevacizumab, patients 65 years of age or older had a higher incidence (≥ 5%) of the following treatment-related adverse events compared to patients younger than 65 years: neutropenia (75.0% vs 65.1%), severe neutropenia (57.0% vs 41.8%), fatigue (39.0% vs 32.2%), thrombocytopenia (28.0% vs 20.5%), and stomatitis (14.0% vs 8.9%).

Infections

In the Phase III placebo-controlled clinical studies, treatment-related infections occurred more frequently in trifluridine/ tipiracil - treated patients (5.8%) compared to those receiving placebo (1.8%). In the clinical study in combination with bevacizumab, treatment-related infections occurred similarly in patients who received trifluridine/ tipiracil with bevacizumab (2.8%) compared to trifluridine/ tipiracil -treated patients (2.4%).

Proteinuria

In the Phase III placebo-controlled clinical studies, treatment-related proteinuria occurred more frequently in trifluridine/ tipiracil -treated patients (1.8%) compared to those receiving placebo (0.9%), all of which were Grade 1 or 2 in severity (see section 4.4).

In the clinical study in combination with bevacizumab, one patient who received trifluridine/ tipiracil with bevacizumab (0.4%) reported a treatment-related proteinuria which was Grade 2 and none among the trifluridine/ tipiracil -treated patients (see section 4.4).

Radiotherapy

There was a slightly higher incidence of overall haematological and myelosuppression-related adverse reactions for patients who received prior radiotherapy compared to patients without prior radiotherapy in RECOURSE (54.6% versus 49.2%, respectively), of note febrile neutropenia was higher in trifluridine/ tipiracil -treated patients who received prior radiotherapy vs. those that did not.

In the clinical study in combination with bevacizumab, no increase of incidence of overall haematological and myelosuppression-related adverse reactions was observed for patients who received prior radiotherapy compared to patients without prior radiotherapy in both arms in SUNLIGHT: trifluridine/ tipiracil with bevacizumab (73.7% versus 77.4%) and in trifluridine/ tipiracil-treated patients (64.7% versus 67.7%).

Post-marketing experience in patients with unresectable advanced or recurrent colorectal cancer

There have been reports of interstitial lung disease in patients receiving trifluridine/ tipiracil post approval.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

The highest dose of trifluridine/ tipiracil administered in clinical studies was 180 mg/m^2

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/ 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

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents,

antimetabolites, ATC code: L01BC59 Mechanism of action

Trifluridine/ 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 (weight ratio, 1:0.471).

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.

Pharmacodynamic effects

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

Clinical efficacy and safety

Metastatic colorectal cancer

Randomised phase III study of trifluridine/ tipiracil *as monotherapy versus placebo*

The clinical efficacy and safety of trifluridine/ tipiracil were evaluated in an international, randomised, double- blind, placebo-controlled Phase III study (RECOURSE) in patients with previously treated metastatic colorectal cancer. The primary efficacy endpoint was overall survival (OS), and supportive efficacy endpoints were progression-free survival (PFS), overall response rate (ORR) and disease control rate (DCR).

In total, 800 patients were randomised 2:1 to receive trifluridine/ tipiracil (N = 534) plus best supportive care (BSC) or matching placebo (N = 266) plus BSC. Trifluridine/ Tipiracil dosing was based on BSA with a starting dose of 35 mg/m^2/dose. Study treatment was administered orally twice daily after morning and evening meals for 5 days a week with 2-day rest for 2 weeks, followed by 14-day rest, repeated every 4 weeks. Patients continued therapy until disease progression or unacceptable toxicity (see section 4.2).

Of the 800 randomised patients, the median age was 63 years, 61% were male, 58% were Caucasian/White, 35% were Asian/Oriental, and 1% were Black/African American, and all patients had baseline Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 or 1. The primary site of disease was colon (62%) or rectum (38%). KRAS status was wild (49%) or mutant (51%) at study entry. The median number of prior lines of therapy for metastatic disease was 3. All patients received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy. All but 1 patient received bevacizumab, and all but 2 patients with KRAS wild type tumours received panitumumab or cetuximab. The 2 treatment groups were comparable with respect to demographic and baseline disease characteristics.

An OS analysis of the study, carried out as planned at 72% (N = 574) of events, demonstrated a clinically meaningful and statistically significant survival benefit of trifluridine/ tipiracil plus BSC compared to placebo plus BSC (hazard ratio: 0.68; 95% confidence interval [CI] [0.58 to 0.81]; p < 0.0001) and a median OS of 7.1 months vs 5.3 months, respectively; with 1-year survival rates of 26.6% and 17.6%, respectively. PFS was significantly improved in patients receiving trifluridine/ tipiracil plus BSC (hazard ratio: 0.48; 95% CI [0.41 to 0.57]; p < 0.0001 (see Table 7, Figure 1 and Figure 2).

Table 7 - Efficacy results from the Phase III (RECOURSE) clinical study in patients with metastatic colorectal cancer

	Trifluridine/ tipiracil plus BSC (N=534)	**Placebo plus BSC (N=266)**
Overall survival		
Number of deaths, N (%)	364 (68.2)	210 (78.9)
Median OS (months)[a] [95% CI][b]	7.1 [6.5, 7.8]	5.3 [4.6, 6.0]
Hazard ratio [95% CI]	0.68 [0.58, 0.81]	
P-value[c]	< 0.0001 (1-sided and 2-sided)	
Progression-Free Survival		

Number of progression or death, N (%)	472 (88.4)	251 (94.4)
Median PFS (months)[a] [95% CI][b]	2.0 [1.9, 2.1]	1.7 [1.7, 1.8]
Hazard ratio [95% CI]	0.48 [0.41, 0.57]	
P-value[c]	<0.0001 (1-sided and 2-sided)	

[a] Kaplan-Meier estimates
[b] Methodology of Brookmeyer and Crowley
[c] Stratified log-rank test (strata: KRAS status, time since diagnosis of first metastasis, region)

Figure 1- Kaplan-Meier curves of overall survival in patients with metastatic colorectal cancer (RECOURSE)

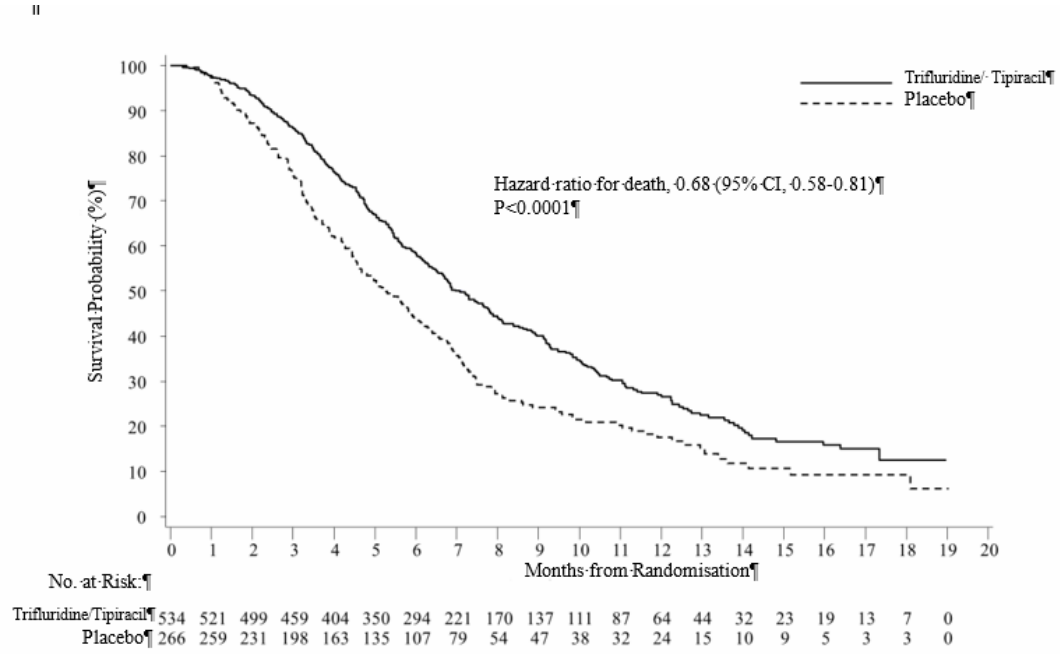
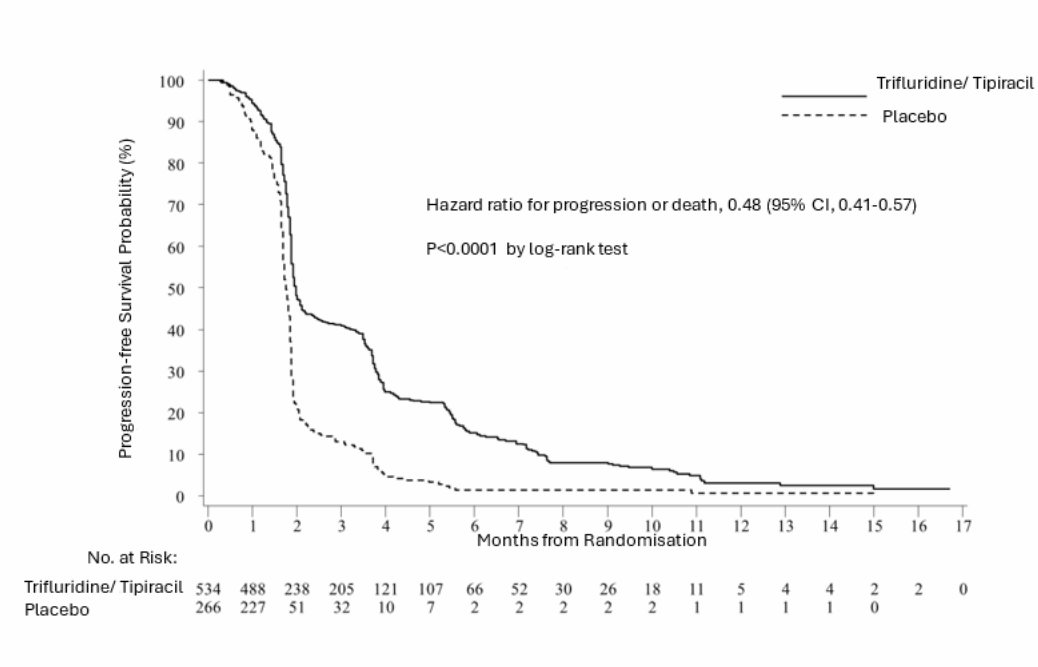


Figure 2 - Kaplan-Meier curves of progression-free survival in patients with metastatic colorectal cancer (RECOURSE)



An updated OS analysis, carried out at 89% (N = 712) of events, confirmed the clinically meaningful and statistically significant survival benefit of trifluridine/ tipiracil plus BSC compared to placebo plus BSC (hazard ratio: 0.69; 95% CI [0.59 to 0.81]; $p < 0.0001$) and a median OS of 7.2 months vs 5.2 months; with 1-year survival rates of 27.1% and 16.6%, respectively.

The OS and PFS benefit was observed consistently, in all relevant pre-specified subgroups, including race, geographic region, age (< 65; ≥ 65), sex, ECOG PS, KRAS status, time since diagnosis of first metastasis, number of metastatic sites, and primary tumour site. The trifluridine/ tipiracil survival benefit was maintained after adjusting for all significant prognostic factors, namely, time since diagnosis of first metastasis, ECOG PS and number of metastatic sites (hazard ratio: 0.69; 95% CI [0.58 to 0.81]).

Sixty one percent (61%, N = 485) of all randomised patients received a fluoropyrimidine as part of their last treatment regimen prior to randomisation, of which 455 (94%) were refractory to the fluoropyrimidine at that time. Among these patients, the OS benefit with trifluridine/ tipiracil was maintained (hazard ratio: 0.75, 95% CI [0.59 to 0.94]).

Eighteen percent (18%, N = 144) of all randomised patients received regorafenib prior to randomisation. Among these patients, the OS benefit with trifluridine/ tipiracil was maintained (hazard ratio: 0.69, 95% CI [0.45 to 1.05]). The effect was also maintained in regorafenib-naive patients (hazard ratio: 0.69, 95% CI [0.57 to 0.83]).

The DCR (complete response or partial response or stable disease) was significantly higher in patients treated with trifluridine/ tipiracil (44% vs 16%, $p < 0.0001$).

Treatment with trifluridine/ tipiracil plus BSC resulted in a statistically significant prolongation of PS <2 in comparison to placebo plus BSC. The median time to PS ≥ 2 for the trifluridine/ tipiracil group and placebo group was 5.7 months and 4.0 months, respectively, with a hazard ratio of 0.66 (95% CI: [0.56, 0.78]),

$p < 0.0001$.

Randomised phase III study of trifluridine/ tipiracil in combination with bevacizumab versus trifluridine/ tipiracil

The clinical efficacy and safety of trifluridine/ tipiracil in combination with bevacizumab, versus trifluridine/ tipiracil monotherapy, were evaluated in an international, randomised, open-label, phase III study (SUNLIGHT) in patients with metastatic colorectal cancer who had been previously treated with a maximum of two prior systemic treatment regimens for advanced disease, including a fluoropyrimidine, irinotecan, oxaliplatin, an anti-VEGF monoclonal antibody and/or an anti-EGFR monoclonal antibody for patients with a RAS wild type tumour. The primary efficacy endpoint was overall survival (OS) and the key secondary efficacy endpoint was progression-free survival (PFS).

In total, 492 patients were randomised (1:1) to receive trifluridine/ tipiracil with bevacizumab (N = 246) or trifluridine/ tipiracil monotherapy (N = 246).

Patients received trifluridine/ tipiracil (starting dose of 35 mg/m^2) administered orally twice daily on Days 1 to 5 and Days 8 to 12 of each 28-day cycle alone or combined with bevacizumab (5 mg/kg) administered intravenously every 2 weeks (on days 1 and 15) of each 4-week cycle. Patients continued therapy until disease progression or unacceptable toxicity (see section 4.2). Bevacizumab monotherapy was not allowed. Baseline characteristics were generally balanced between the two groups. The median age was 63 years (range: 20-90), with 44% ≥ 65 years of age and 12% ≥ 75 years of age, 52% of patients were male and 95% were white, 46% had ECOG PS 0 and 54% had ECOG PS 1. The primary site of disease was colon (73%) or rectum (27%). Overall, 71% of the patients had a RAS mutant tumour. The median duration of treatment was 5 months in the trifluridine/ tipiracil-bevacizumab group and 2 months in the trifluridine/ tipiracil group. A total of 92% of patients received two prior anticancer treatment regimens for advanced CRC, 5% received one and 3% received more than two. All patients received prior fluoropyrimidine, irinotecan and oxaliplatin, 72% received prior anti-VEGF monoclonal antibody,94% of patients with a RAS wild type tumour received prior anti-EGFR monoclonal antibody.

Trifluridine/ tipiracil in combination with bevacizumab resulted in a statistically significant improvement in OS and PFS compared to trifluridine/ tipiracil monotherapy (see Table 8 and Figures 3 and 4).

Table 8 - Efficacy results from the Phase III (SUNLIGHT) clinical study in patients with metastatic colorectal cancer

	Trifluridine/ tipiracil plus bevacizumab (N=246)	**Trifluridine/ tipiracil (N=246)**
Overall survival		
Number of deaths, N (%)	148 (60.2)	183 (74.4)
Median OS (months)[a] [95% CI][b]	10.8 [9.4, 11.8]	7.5 [6.3, 8.6]
Hazard ratio [95% CI]	0.61 [0.49, 0.77]	
P-value[c]	< 0.001 (1-sided)	

Progression-free survival (per investigator)		
Number of progression or death, N (%)	206 (83.7)	236 (95.9)
Median PFS (months)[a] [95% CI][b]	5.6 [4.5, 5.9]	2.4 [2.1, 3.2]
Hazard ratio [95% CI]	0.44 [0.36, 0.54]	
P-value[c]	< 0.001 (1-sided)	

[a] Kaplan-Meier estimates
[b] Methodology of Brookmeyer and Crowley
[c] Stratified log-rank test (strata: region, time since first metastasis diagnosis, RAS status)

Figure 3- Kaplan-Meier curves of overall survival in patients with metastatic colorectal cancer (SUNLIGHT)

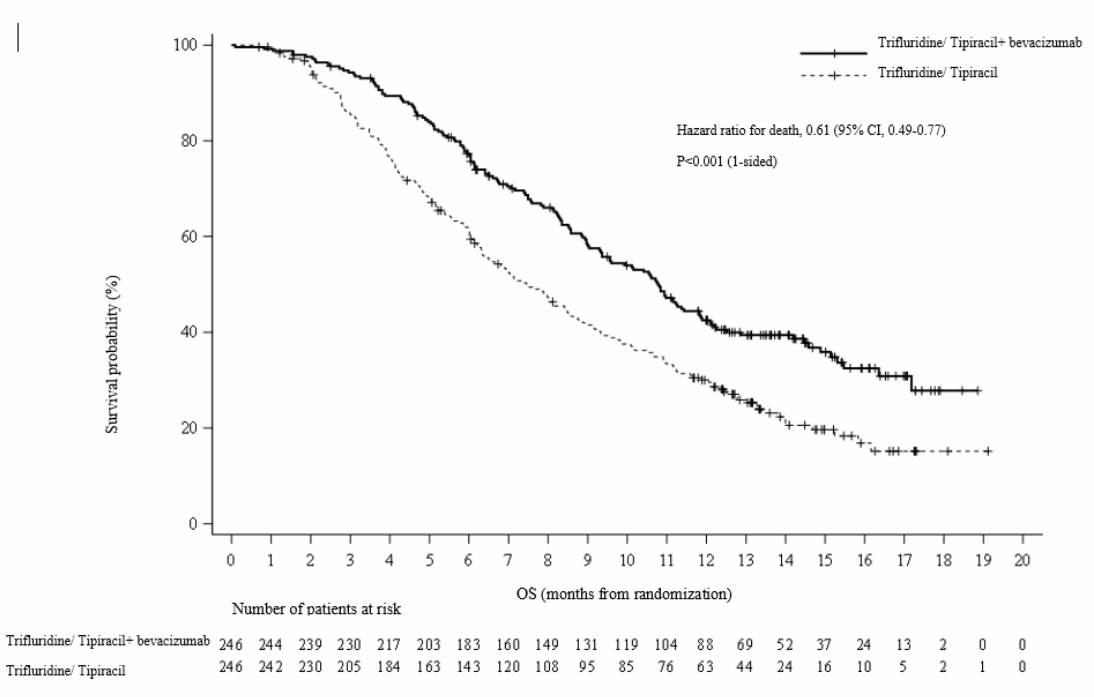
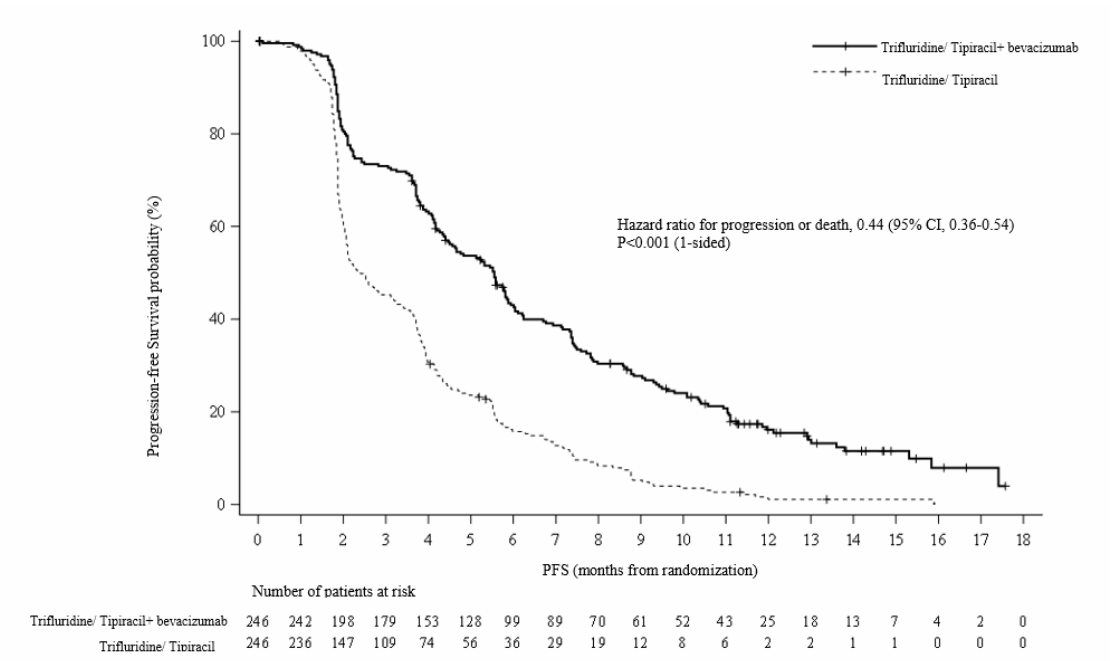


Figure 4 - Kaplan-Meier curves of progression-free survival in patients with metastatic colorectal cancer (SUNLIGHT)



The OS and PFS benefit was observed consistently, in all randomization strata and pre specified subgroups, including gender, age (< 65, ≥ 65 years), location of

primary disease (right, left), ECOG performance status (0, ≥1), prior surgical resection, number of metastatic sites (1-2, ≥ 3), neutrophils to lymphocytes ratio (NLR< 3, NLR ≥ 3), number of prior metastatic drug regimens (1, ≥ 2), BRAF status, MSI status, prior bevacizumab and subsequent regorafenib.

Metastatic gastric cancer

The clinical efficacy and safety of trifluridine/ tipiracil were evaluated in an international, randomised, double- blind, placebo-controlled Phase III study (TAGS) in patients with previously treated metastatic gastric cancer (including adenocarcinoma of the gastroesophageal junction), who had been previously treated with at least two prior systemic treatment regimens for advanced disease, including fluoropyrimidine-, platinum-, and either taxane- or irinotecan-based chemotherapy, plus if appropriate human epidermal growth factor receptor 2 (HER2) -targeted therapy. The primary efficacy endpoint was overall survival (OS), and supportive efficacy endpoints were progression-free survival (PFS), overall response rate (ORR), disease control rate (DCR), time to deterioration of ECOG performance status ≥2 and quality of life (QoL). Tumour assessments, according to the Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1, were performed by the investigator/local radiologist every 8 weeks.

In total, 507 patients were randomised 2:1 to receive trifluridine/ tipiracil (N = 337) plus best supportive care (BSC) or placebo (N = 170) plus BSC. trifluridine/ tipiracil dosing was based on BSA with a starting dose of 35 mg/m^2/dose. Study treatment was administered orally twice daily after morning and evening meals for 5 days a week with 2-day rest for 2 weeks, followed by 14-day rest, repeated every 4 weeks. Patients continued therapy until disease progression or unacceptable toxicity (see section 4.2).

Of the 507 randomised patients, the median age was 63 years, 73% were male, 70% were White, 16% were Asian, and <1% were Black/African American, and all patients had baseline Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 or 1. Primary cancer was gastric (71.0%) or gastroesophageal junction cancer (28.6%) or both (0.4%). The median number of prior regimens of therapy for metastatic disease was 3. Nearly all (99.8%) patients received prior fluoropyrimidine, 100% received prior platinum therapy and 90.5% received prior taxane therapy. Approximately half (55.4%) of patients received prior irinotecan, 33.3% received prior ramucirumab, and 16.6% received prior HER2-targeted therapy. The 2 treatment groups were comparable with respect to demographic and baseline disease characteristics.

An OS analysis of the study, carried out as planned at 76% (N = 384) of events, demonstrated that trifluridine/ tipiracil plus BSC resulted in a statistically significant improvement in OS compared to placebo plus BSC with an hazard ratio (HR) of 0.69 (95% CI: 0.56, 0.85; 1- and 2-sided p-values were 0.0003 and 0.0006, respectively) corresponding to a 31% reduction in the risk of death in the trifluridine/ tipiracil group. The median OS was 5.7 months (95% CI: 4.8, 6.2) for the trifluridine/ tipiracil group versus 3.6 months (95% CI: 3.1, 4.1) for the placebo group; with 1-year survival rates of 21.2% and 13.0%, respectively.

PFS was significantly improved in patients receiving trifluridine/ tipiracil plus BSC compared to placebo plus BSC (HR of 0.57; 95% CI [0.47 to 0.70]; $p < 0.0001$ (see Table 9, Figure 5 and Figure 6).

Table 9 - Efficacy results from the Phase III (TAGS) clinical study in patients with metastatic gastric cancer

	Trifluridine/ tipiracil plus BSC (N=337)	Placebo plus BSC (N=170)
Overall survival		
Number of deaths, N (%)	244 (72.4)	140 (82.4)
Median OS (months)[a] [95% CI][b]	5.7 [4.8, 6.2]	3.6 [3.1, 4.1]
Hazard ratio [95% CI]	0.69 [0.56, 0.85]	
P-value[c]	0.0003 (1-sided), 0.0006 (2-sided)	
Progression-Free Survival		
Number of progression or death, N (%)	287 (85.2)	156 (91.8)
Median PFS (months)[a] [95% CI][b]	2.0 [1.9, 2.3]	1.8 [1.7, 1.9]
Hazard ratio [95% CI]	0.57 [0.47, 0.70]	
P-value[c]	<0.0001 (1-sided and 2-sided)	

[a] Kaplan-Meier estimates

[b] Methodology of Brookmeyer and Crowley

[c] Stratified log-rank test (strata: region, ECOG status at baseline, prior ramucirumab treatment)

Figure 5- Kaplan-Meier curves of overall survival in patients with metastatic gastric cancer (TAGS)

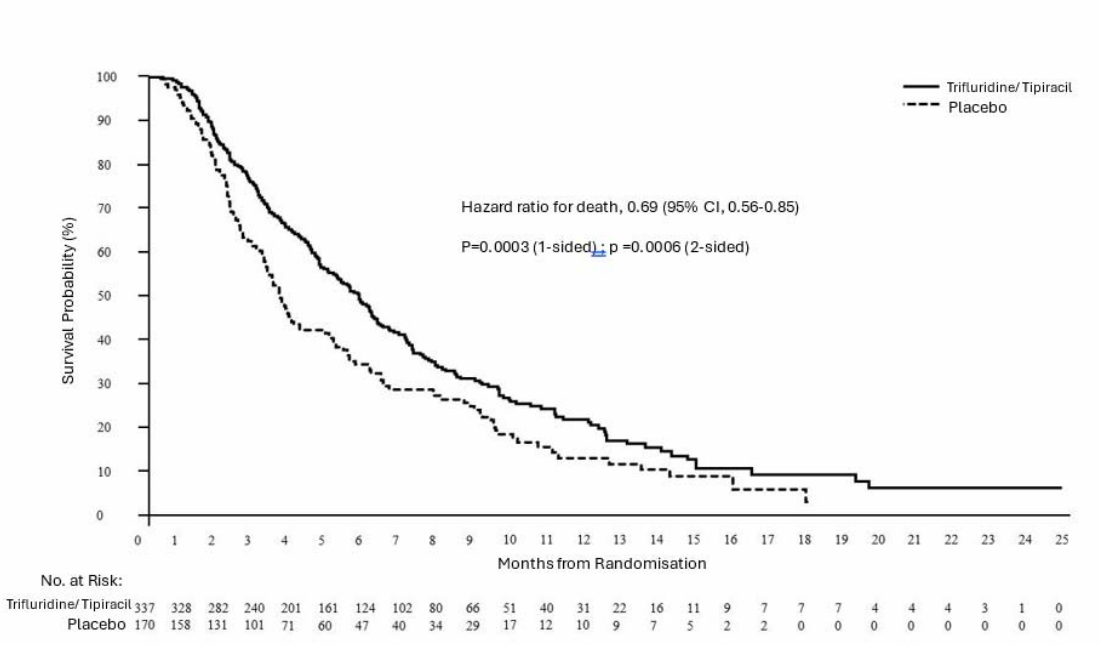
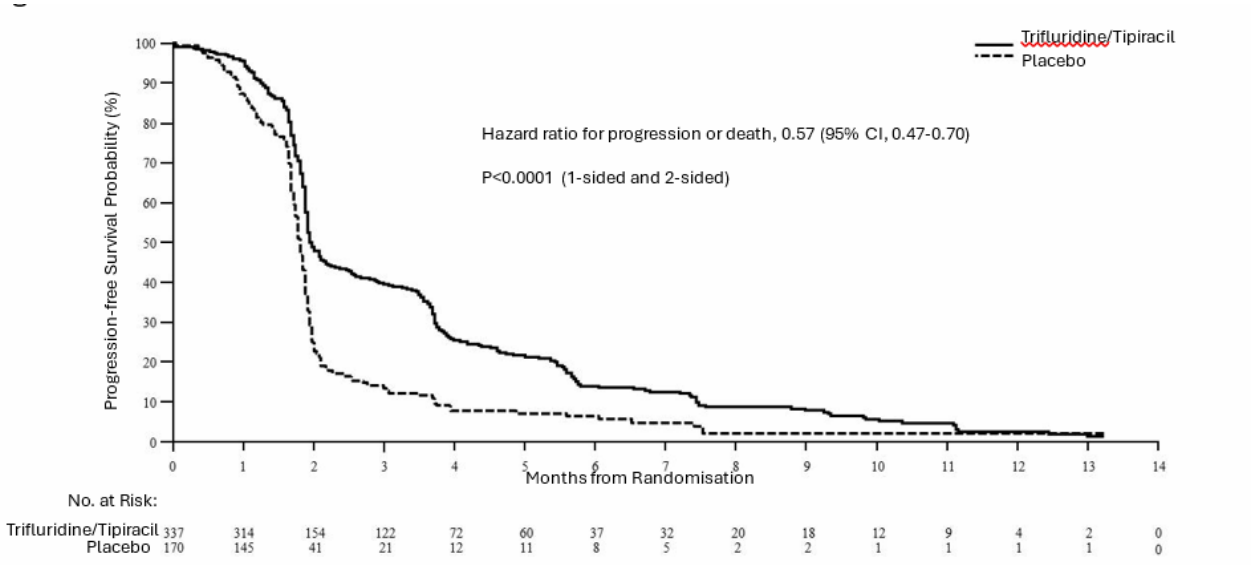


Figure 6 - Kaplan-Meier curves of progression-free survival in patients with metastatic gastric cancer (TAGS)



The OS and PFS benefit was observed consistently, in all randomization strata and across most pre-specified subgroups, including sex, age (< 65; ≥ 65 years), ethnic origin, ECOG PS, prior ramucirumab treatment, prior irinotecan treatment, number of prior regimens (2; 3; ≥ 4), previous gastrectomy, primary tumour site (gastric; gastroesophageal junction) and HER2 status.

The ORR (complete response + partial response) was not significantly higher in patients treated with trifluridine/ tipiracil (4.5% vs 2.1 %, p-value = 0.2833) but the DCR (complete response or partial response or stable disease) was significantly higher in patients treated with trifluridine/ tipiracil (44.1% vs 14.5%, p < 0.0001). The median time to deterioration of ECOG performance status to ≥2 was 4.3 months for the trifluridine/ tipiracil group versus 2.3 months for the placebo group with HR of 0.69 (95% CI: 0.562, 0.854), p-value = 0.0005.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with trifluridine/ tipiracil in all subsets of the paediatric population in refractory metastatic colorectal cancer and in refractory metastatic gastric cancer (see section 4.2 for information on paediatric use).

Elderly

There is limited data in trifluridine/ tipiracil treated patients aged 75 years and above:

-87 patients (10%) in pooled data of the RECOURSE and TAGS studies, of which 2 patients were 85 years or older. The effect of trifluridine/ tipiracil on overall survival was similar in patients <65 years and ≥65 years of age.

- 58 patients (12%) were aged 75 years and above, of which 1 patient was 85 years or older in the SUNLIGHT study. The effect of trifluridine/ tipiracil in combination with bevacizumab on overall survival was similar in patients < 65 years and ≥ 65 years of age.

5.2 Pharmacokinetic properties

Absorption

After oral administration of trifluridine/ tipiracil with [^{14}C]-trifluridine, at least 57% of the administered trifluridine was absorbed and only 3% of the dose was excreted into faeces. After oral administration of trifluridine/ 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 faeces, suggestive of moderate gastrointestinal absorption of tipiracil hydrochloride. Following a single dose of trifluridine/ tipiracil (35 mg/m^2) in patients with advanced solid tumours, the mean times to peak plasma concentrations (tmax) 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/ tipiracil (35 mg/m^2/dose, twice daily for 5 days a week with 2-day 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/ 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/ tipiracil. Following multiple doses of trifluridine/ tipiracil (35 mg/m^2/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.

Contribution of tipiracil hydrochloride

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

Effect of food

When trifluridine/ tipiracil at a single dose of 35 mg/m^2 was administered to 14 patients with solid tumours after a standardised high-fat, high-calorie meal, trifluridine area under the concentration-time curve (AUC) did not change, but trifluridine C_{max}, tipiracil hydrochloride C_{max} and AUC decreased by approximately 40% compared to those in a fasting state. In clinical studies trifluridine/ tipiracil was administered within 1 hour after completion of the morning and evening meals (see section 4.2).

Distribution

The protein binding of trifluridine in human plasma was over 96% and trifluridine bound mainly to human serum albumin. Plasma protein binding of tipiracil hydrochloride was below 8%. Following a single dose of trifluridine/ tipiracil (35 mg/m^2) in patients with advanced solid tumours, the apparent volume of distribution (Vd/F) for trifluridine and tipiracil

hydrochloride was 21 L and 333 L, respectively.

Biotransformation

Trifluridine was mainly eliminated by metabolism via TPase to form an inactive metabolite, FTY. The absorbed trifluridine was metabolised, and excreted into urine as FTY and trifluridine glucuronide isomers. Other minor metabolites, 5-carboxyuracil and 5-carboxy-2'-deoxyuridine, were detected, but those levels in plasma and urine were at low or trace levels.

Tipiracil hydrochloride was not metabolised in human liver S9 or in cryopreserved human hepatocytes. Tipiracil hydrochloride was the major component and 6-hydroxymethyluracil was the major metabolite consistently in human plasma, urine, and faeces.

Elimination

Following the multiple-dose administration of trifluridine/ tipiracil at the recommended dose and regimen, the mean elimination half-life ($t_{1/2}$) for trifluridine on Day 1 of Cycle 1 and on Day 12 of Cycle 1 were 1.4 hours and 2.1 hours, respectively. The mean $t_{1/2}$ values for tipiracil hydrochloride on Day 1 of Cycle 1 and on Day 12 of Cycle 1 were 2.1 hours and 2.4 hours, respectively.

Following a single dose of trifluridine/ tipiracil (35 mg/m^2) in patients with advanced solid tumours, the oral clearance (CL/F) for trifluridine and tipiracil hydrochloride were 10.5 L/hr and 109 L/hr, respectively. After single oral administration of trifluridine/ tipiracil 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) within 24 hours, and the excretion into faeces and expired air was less than 3% for both. After single oral administration of trifluridine/ tipiracil with [^{14}C]-tipiracil hydrochloride, recovered radioactivity was 77% of the dose, which consisted of 27% urinary excretion and 50% faecal excretion.

Linearity/non-linearity

In a dose finding study (15 to 35 mg/m^2 twice daily), the AUC from time 0 to 10 hours (AUC_{0-10}) of trifluridine tended to increase more than expected based on the increase in dose; however, oral clearance (CL/F) and apparent volume of distribution (Vd/F) of trifluridine were generally constant at the dose range of 20 to 35 mg/m^2. As for the other exposure parameters of trifluridine and tipiracil hydrochloride, those appeared to be dose proportional.

Pharmacokinetics in special populations

Age, gender and race

Based on the population PK analysis, there is no clinically relevant effect of age, gender or race on the PK of trifluridine or tipiracil hydrochloride.

Renal impairment

Of the 533 patients in the RECOURSE study who received trifluridine/ tipiracil, 306 (57%) patients had normal renal function (CrCl ≥ 90 mL/min), 178 (33%) patients had mild renal impairment (CrCl 60 to 89 mL/min), and 47

(9%) had moderate renal impairment (CrCl 30 to 59 mL/min), with data missing for 2 patients. Patients with severe renal impairment were not enrolled in the study.

Based on a population PK analysis, the exposure of trifluridine/ tipiracil in patients with mild renal impairment (CrCl = 60 to 89 mL/min) was similar to those in patients with normal renal function (CrCl ≥ 90 mL/min). A higher exposure of trifluridine/ tipiracil was observed in moderate renal impairment (CrCl = 30 to 59 mL/min). Estimated (CrCl) was a significant covariate for CL/F in both final models of trifluridine and tipiracil hydrochloride. The mean relative ratio of AUC in patients with mild (n=38) and moderate (n=16) renal impairment compared to patients with normal renal function (n=84) were 1.31 and 1.43 for trifluridine, respectively, and 1.34 and 1.65 for tipiracil hydrochloride, respectively.

In a dedicated study the pharmacokinetics of trifluridine and tipiracil hydrochloride were evaluated in cancer patients with normal renal function (CrCl ≥90 mL/min, N=12), mild renal impairment (CrCl =60 to 89 mL/min, N=12), moderate renal impairment (CrCl =30 to 59 mL/min, N=11), or severe renal impairment (CrCl =15 to 29 mL/min, N=8). Patients with severe renal impairment received an adjusted starting dose of 20 mg/m^2 twice daily (reduced to 15 mg/m^2 twice daily based on individual safety and tolerability). The effect of renal impairment after repeated administration was a 1.6- and 1.4-fold increase of trifluridine total exposure in patients with moderate and severe renal impairment, respectively, compared to patients with normal renal function; C_{max} remained similar. The total exposure of tipiracil hydrochloride in patients with moderate and severe renal impairment after repeated administration was 2.3- and 4.1-fold higher, respectively, compared to patients with normal renal function; this being linked to a more decreased clearance with increasing renal impairment. The PK of trifluridine and tipiracil hydrochloride have not been studied in patients with end-stage f disease (CrCl < 15 mL/min or requiring dialysis) (see sections 4.2 and 4.4).

Hepatic impairment

Based on the population PK analysis, liver function parameters including alkaline phosphatase (ALP, 36-2322 U/L), aspartate aminotransferase (AST, 11-197 U/L), alanine aminotransferase (ALT, 5-182 U/L), and total bilirubin (0.17-3.20 mg/dL) were not significant covariates for PK parameters of either trifluridine or tipiracil hydrochloride. Serum albumin was found to significantly affect trifluridine clearance, with a negative correlation. For low albumin values ranging from 2.2 to 3.5 g/dL, the corresponding clearance values range from 4.2 to 3.1 L/h.

In a dedicated study the PK of trifluridine and tipiracil hydrochloride were evaluated in cancer patients with mild or moderate hepatic impairment (National C dysgeusia ancer Institute [NCI] Criteria Group B and C, respectively) and in patients with normal hepatic function. Based upon limited data with a considerable variability, no statistically significant differences were observed in the pharmacokinetics in patients with normal hepatic function versus patients with mild or moderate hepatic impairment. No correlation was seen for trifluridine nor tipiracil hydrochloride between PK parameters and AST or/and total blood bilirubin. Half-life time ($t_{1/2}$) and the accumulation ratio of trifluridine and tipiracil hydrochloride were similar between the moderate, mild and normal hepatic function patients.

There is no need for a starting dose adjustment in patients with mild hepatic impairment (see section 4.2).

Gastrectomy

The influence of gastrectomy on PK parameters was not able to be examined in the population PK analysis because there were few patients who had undergone gastrectomy (1% of overall).

In vitro interaction studies

Trifluridine is a substrate of TPase, but is not metabolised by cytochrome P450 (CYP). Tipiracil hydrochloride is not metabolised in either human liver S9 or cryopreserved hepatocytes.

In vitro studies indicated that trifluridine, tipiracil hydrochloride and FTY (inactive metabolite of trifluridine) did not inhibit the CYP isoforms tested (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4/5). *In vitro* evaluation indicated that trifluridine, tipiracil hydrochloride and FTY had no inductive effect on human CYP1A2, CYP2B6 or CYP3A4/5. Thus trifluridine and tipiracil hydrochloride are not expected to cause or be subject to a significant medicinal product interaction mediated by CYP.

In vitro evaluation of trifluridine and tipiracil hydrochloride was conducted using human uptake and efflux transporters (trifluridine with MDR1, OATP1B1, OATP1B3 and BCRP; tipiracil hydrochloride with OAT1, OAT3, OCT2, MATE1, MDR1 and BCRP). Neither trifluridine nor tipiracil hydrochloride was an inhibitor of or substrate for human uptake and efflux transporters based on *in vitro* studies, except for OCT2 and MATE1. Tipiracil hydrochloride was an inhibitor of OCT2 and MATE1 *in vitro*, but at concentrations substantially higher than human plasma C_{max} at steady state.
Thus it is unlikely to cause an interaction with other medicinal products, at recommended doses, due to inhibition of OCT2 and MATE1. Transport of tipiracil hydrochloride by OCT2 and MATE1 might be affected when trifluridine/ tipiracil is administered concomitantly with inhibitors of OCT2 and MATE1.

Pharmacokinetic/pharmacodynamic relationship
The efficacy and safety of trifluridine/ tipiracil in metastatic colorectal cancer was compared between a high-exposure group (>median) and a low-exposure group (≤median) based on the median AUC value of trifluridine. OS appeared more favourable in the high AUC group compared to the low AUC group (median OS of 9.3 vs. 8.1 months, respectively). All AUC groups performed better than placebo throughout the follow-up period. The incidences of Grade ≥3 neutropenia were higher in the high-trifluridine AUC group (47.8%) compared with the low-trifluridine AUC group (30.4%).

5.3 Preclinical safety data

Repeat-dose toxicity

Toxicology assessment of trifluridine/tipiracil hydrochloride was performed in rats, dogs and monkeys. The target organs identified were the lymphatic and

haematopoietic systems and the gastrointestinal tract. All changes, i.e., leukopenia, anaemia, bone marrow hypoplasia, atrophic changes in the lymphatic and haematopoietic 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/ 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/ Tipiracil has been shown to cause embryo-foetal lethality and embryo-foetal toxicity in pregnant rats when given at dose levels lower than the clinical exposure. No peri/post-natal developmental toxicity studies have been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Lactose monohydrate
Starch, pregelatinised (maize)
Stearic acid

Film coating

Trifluridine/ Tipiracil 15 mg/6.14 mg film-coated tablets
Hypromellose
Macrogol (8000)
Titanium dioxide (E171)
Magnesium stearate

Trifluridine/ Tipiracil 20 mg/8.19 mg film-coated tablets
Hypromellose
Macrogol (8000)
Titanium dioxide (E171)
Iron oxide red (E172)
Magnesium stearate

Printing ink
Shellac
Iron oxide red (E172)
Iron oxide yellow (E172)
Titanium dioxide (E171)
Indigo carmine aluminium lake (E132)
Carnauba wax
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium/Aluminium blister with laminated desiccant (calcium oxide) containing 10 tablets.

Each pack contains 20, 40 or 60 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Hands should be washed after handling the tablets.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Les Laboratoires Servier
50 rue Carnot
92284 Suresnes Cedex
France

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 05815/0113

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/01/2021

10 DATE OF REVISION OF THE TEXT

13/04/2026