AUSTRALIAN PI – LONSURF (TRIFLURIDINE/TIPIRACIL)

1 NAME OF THE MEDICINE

Trifluridine / tipiracil hydrochloride

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each LONSURF 15/6.14 film-coated tablet contains 15 mg of trifluridine and tipiracil hydrochloride 7.065 mg (equivalent to tipiracil 6.14 mg). Each LONSURF 20/8.19 film-coated tablet contains 20 mg of trifluridine and tipiracil hydrochloride 9.420 mg (equivalent to tipiracil 8.19 mg).

The active components of LONSURF are trifluridine and tipiracil hydrochloride.

Excipients with known effect:

Each LONSURF 15/6.14 tablet contains 90.735 mg of lactose.

Each LONSURF 20/8.19 tablet contains 120.980 mg of lactose.

For the full list of excipients, see *section 6.1 - List of excipients*.

3 PHARMACEUTICAL FORM

LONSURF 15/6.14: white, biconvex, round, film-coated tablet, imprinted with ‘15’ on one side, and ‘102’ and ’15 mg’ on the other side, in grey ink.

LONSURF 20/8.19: pale red, biconvex, round, film-coated tablet, 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

LONSURF is indicated for the treatment of adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with, or are not considered candidates for fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents.

Gastric cancer

LONSURF 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 DOSE AND METHOD OF ADMINISTRATION

Dosage (dose and interval)

LONSURF must be administered by doctors who are familiar with the use of antineoplastic medicines and have the facilities for regular monitoring of clinical, haematological, and biochemical parameters during and after treatment.

Complete blood cell counts must be taken prior to initiation of each cycle.

Dose

The recommended starting dose of LONSURF in adults is 35 mg/m^2/dose (based on the trifluridine component) administered orally twice daily on Days 1 to 5 and Days 8 to 12 of each 28-day cycle as long as benefit is observed or until unacceptable toxicity occurs (see *section 4.4 - Special Warnings and Precautions for Use*).

The LONSURF dose is calculated according to body surface area (BSA). Do not exceed 80 mg/dose.

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

Starting dose

Table 1 – Starting dose calculation according to body surface area (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

Dose modification guidelines

Dosing adjustments may be required based on individual safety and tolerability.

A maximum of 3 dose reductions to a minimum dose of 20 mg/m^2 twice daily, are permitted. 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 below.

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

Parameter	Interruption criteria	Resumption criteria[a]
Neutrophils	$< 0.5 \times 10^9$/L	$\geq 1.5 \times 10^9$/L
Platelets	$< 50 \times 10^9$/L	$\geq 75 \times 10^9$/L

[a] 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 LONSURF in case of haematological and non-haematological adverse reactions

Adverse reaction	Recommended dose modifications
• Febrile neutropenia • CTCAE* Grade 4 neutropenia ($< 0.5 \times 10^9$/L) or thrombocytopenia ($< 25 \times 10^9$/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 anti-diarrhoeal 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 body surface area (BSA)

Reduced dose	BSA (m^2)	Dose in mg (2x daily)	Tablets per dose (2x daily) 15 mg/6.14 mg	20 mg/8.19 mg	Total daily dose (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/m2 to 25 mg/m2					
	< 1.10	25[a]	2[a]	1[a]	50[a]

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	
25 mg/m^2	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/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.

Method of Administration

LONSURF should be administered orally twice daily on Days 1 to 5 and Days 8 to 12 of each 28-day cycle as long as benefit is observed or until unacceptable toxicity occurs (see *section -4.4 Special Warnings and Precautions for Use).*

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

Special precautions for disposal

Hands should be washed after handling tablets.

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

Dosage adjustment

Patients with impaired renal function

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 - Special warnings and precautions for use & 5.2 - Pharmacokinetic Properties*).

Patients with moderate renal impairment (CrCl = 30 to 59 mL/min) at baseline had a higher incidence (defined as a difference of at least 5 %) of ≥ Grade 3 adverse events (AEs), serious AEs, and

dose delays and reductions compared to the patients with normal (CrCl ≥ 90 mL/min) or mild renal impairment (CrCl = 60 to 89 mL/min) at baseline. In addition, a higher exposure of trifluridine and tipiracil was observed in patients with moderate renal impairment at baseline, compared with patients with normal renal function or patients with mild renal impairment at baseline (see *section 5.1 - Pharmacodynamic Properties*). Patients with moderate renal impairment should be more frequently monitored for haematological toxicities and may require dose adjustment (see *section 4.2 - Dose And Method of Administration- 'Dose modification guidelines'*).

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 *Special warnings and precautions for use* and 5.2 *Pharmacokinetic Properties*). 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 body surface area (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 15mL/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 Special warnings and precautions for use*).

Patients with impaired hepatic function

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

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 - Special Warnings and Precautions for Use & 5.2 - Pharmacokinetic Properties*).

Paediatric population

The safety and efficacy of LONSURF in children aged < 18 years has not yet been established. No data are available.

Elderly patients

No specific dose adjustment is required in elderly patients (aged ≥ 65 years). Efficacy and safety data in patients aged >75 years is limited.

Ethnicity

No adjustment of the starting dose is required on the basis of patient's race. There is limited data on LONSURF in African American patients but there is no biological rationale to expect any difference between this subgroup and the overall population.

4.3 CONTRAINDICATIONS

LONSURF is contraindicated in patients with a history of previous hypersensitivity to tipiracil, trifluridine or any of the excipient ingredients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

The safety of LONSURF has not been studied in patients with mCRC with an Eastern Cooperative Oncology Group (ECOG) performance status ≥ 2.

Bone marrow suppression

In the 868 patients who received LONSURF in RECOURSE and TAGS, LONSURF caused severe and life-threatening myelosuppression (Grade 3-4) consisting of anaemia (12.1 %), neutropenia (34.1 %), thrombocytopenia (3.7 %) 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 LONSURF-treated patients received granulocyte-colony stimulating factors.

For cycle 1, consider clinical review and FBC on day 15 and then as clinically indicated. Thereafter obtain complete blood counts prior to each cycle of LONSURF and more frequently as clinically

indicated. Withhold LONSURF for severe myelosuppression and resume at the next lower dosage (see s*ection - 4.2 Dose and Method of Administration)*.

Serious infections have been reported following treatment with LONSURF (see *section 4.8 - Adverse Effects (Undesirable Effects)*). 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 medicines and Granulocyte-Colony Stimulating Factor (G-CSF), should be administered as clinically indicated. In RECOURSE, TAGS and SUNLIGHT studies (see *section 5.0 Pharmacodynamic Properties*), 9.4%, 17.3% and 19.5% of patients in the LONSURF group respectively received G-CSF mainly for therapeutic use. In the SUNLIGHT study, 29.3% of patients in the LONSURF with bevacizumab group received G-CSF including 16.3% for therapeutic use.

Gastrointestinal Toxicity

LONSURF 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. Appropriate measures such as antiemetic, anti-diarrhoeal, and/or 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 - Dose And Method of Administration*).

Lactose intolerance

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

Use in hepatic impairment

LONSURF 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 - Pharmacokinetic Properties*).

Use in renal impairment

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

In RECOURSE, patients with moderate renal impairment (CrCl = 30 to 59 mL/min) had a higher incidence (defined as a difference of at least 5 %) of ≥ Grade 3 adverse events (AEs), serious AEs, and dose delays and reductions compared to the patients with normal renal function (CrCl ≥ 90 mL/min) or mild renal impairment (CrCl = 60 to 89 mL/min). In TAGS, there was no marked difference between the normal renal function, the mild and the moderate renal impairment subgroups (based on baseline CrCl) with respect to overall incidence of AEs, ≥ Grade 3 AEs or serious AEs, dose delays and reductions. However, several of the most frequently reported AEs increased with the degree of renal impairment (anaemia, neutropenia, decreased appetite and diarrhoea) and patients with

moderate impairment had higher incidences of Grade 3 and 4 abnormalities for haemoglobin and leukocytes compared to normal and mild impairment subgroups.

In addition, a higher exposure of trifluridine and tipiracil 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 - Pharmacokinetic Properties*).

Patients with severe renal impairment (CrCl = 15 to 29 mL/min) and adjusted starting dose of 20 mg/m^2 twice daily had a safety profile consistent with the safety profile of Lonsurf 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 *section 4.2 Dose And Method of Administration* and *section 5.2 Pharmacokinetic Properties*).

Patients with moderate or severe renal impairment should be monitored more frequently for haematological toxicities.

Use in the Elderly

No adjustment of the recommended starting dose of LONSURF is required for patients aged ≥ 65 years. Efficacy and safety data in patients aged > 75 years are limited.

Paediatric Use

Use of LONSURF in children aged < 18 years is not recommended as no data establishing safety or effectiveness in children are available. When trifluridine/tipiracil (molar ratio 1:0.5) was administered orally once daily to rats at 5, 15, 50 and 150 mg trifluridine/kg for 13 weeks, incisor abnormalities, such as whitening, breakage and malocclusion were observed at ≥ 50 mg trifluridine/kg/day (approximately two times the clinical exposure, based on AUC, at the clinical dose of 35 mg/m^2 twice daily).

As the incisors of rats continuously grow (a normal growing incisor is renewed every 40-50 days), it can be supposed that such effects were produced by altered odontogenic epithelium after administration of trifluridine/tipiracil. Therefore, the changes seen at the upper or at the lower part of the dental shaft may be considered to be relevant for paediatric patients.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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 - Pharmacokinetic Properties*).

<u>Medicines that are inhibitors of OCT2 or MATE1.</u>

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 LONSURF is administered concomitantly with inhibitors of OCT2 or MATE1.

Medicines that are human thymidine kinase substrates (e.g. zidovudine)

Caution is required when using medicines that are human thymidine kinase substrates, e.g. zidovudine. Such medicines, if used concomitantly with LONSURF, may compete with the effector, trifluridine, for activation via thymidine kinases. Therefore, when using antiviral medicines that are human thymidine kinase substrates, monitor for possible decreased efficacy of the antiviral medicine, and consider switching to an alternative antiviral medicine that is not a human thymidine kinase substrate, such as lamivudine, didanosine, and abacavir.

Hormonal contraceptives

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There are no data available on the effect of LONSURF on human fertility. In a dedicated study in animals, fertility was unaffected in male and female rats dosed with trifluridine/tipiracil (molar ratio 1:0.5) at up to 221mg/kg/day (150 mg trifluridine/kg/day, approximately five times the clinical exposure, based on AUC, at 35 mg/m^2 twice daily). However, the number of viable embryos was decreased at 150 mg/kg/day (no effect at 50 mg/kg/day, approximately two times the clinical exposure), although the number of implantations and corpora lutea were increased at 150 mg/kg/day. In a general toxicity study by repeated dosing, mild atrophy of seminiferous tubules in the testis and decreased sperm counts in the epididymis were observed in rats at 450 mg trifluridine/kg (approximately 17 times the clinical exposure) and increased ovary weights and number of small corpora lutea at ≥150 mg trifluridine/kg/day.

Use in pregnancy

Australian pregnancy categorisation: D

Based on the mechanism of action, trifluridine is suspected to cause congenital malformations when administered during pregnancy. LONSURF has been shown to cause embryo-foetal lethality and foetal malformations in pregnant rats.

LONSURF should not be used during pregnancy and in women of childbearing potential not using contraception. Women and men must use highly effective contraception during and up to 6 months after treatment. Women of childbearing potential and their partners should be advised to avoid pregnancies while taking LONSURF and for up to six months after ending treatment. 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 LONSURF treatment.

There are no data on the use of LONSURF in pregnant women. LONSURF should not be used during pregnancy unless the clinical condition of the woman requires treatment with LONSURF, and if the potential benefit to the mother outweighs the potential risk to the foetus.

It is currently unknown whether LONSURF may reduce the effectiveness of hormonal contraceptives, and therefore women using hormonal contraceptives should add a barrier contraceptive method.

Effects on embryofetal development was assessed in pregnant rats dosed with trifluridine/tipiracil (molar ratio 1:0.5) once daily during organogenesis. Embryolethality and malformations (kinked tail, cleft palate, ectrodactyly, anasarca, alterations in large blood vessels, ventricular septal defect, supernumerary lung lobe, convoluted/dilated ureter, and skeletal anomalies including misaligned sternebrae and sternoschiasis) were observed at 150 mg trifluridine/kg/day (approximately 5 times the clinical exposure, based on AUC, at 35 mg/m^2 twice daily). Decreased fetal weight and skeletal variations (delayed ossification, supernumerary ribs/thoracic vertebrae) were observed at ≥ 50 mg trifluridine/kg (approximately 2 times the clinical exposure).

Use in lactation

It is unknown whether LONSURF or its metabolites are excreted in human milk. Studies in animals have shown excretion of trifluridine, tipiracil hydrochloride and/or their metabolites in milk. A risk to the breast-feeding child cannot be excluded. Breast-feeding should be discontinued during treatment with LONSURF.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

LONSURF might interfere with the ability to drive and operate machinery. Fatigue, dizziness or malaise may occur during treatment (see *section 4.8 - Adverse Effects (Undesirable Effects)*).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Reporting suspected adverse effects

Reporting suspected adverse drug reactions after registration 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 at www.tga.gov.au/reporting-problems.

Summary of the safety profile

LONSURF as monotherapy

The safety profile of LONSURF 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 serious observed adverse drug reactions in patients receiving LONSURF are bone marrow suppression and gastrointestinal toxicity *(*see *section 4.4 - Special Warnings and Precautions for Use)*.

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]).

LONSURF in combination with bevacizumab

The safety profile of LONSURF in combination with bevacizumab is based on the data from 246 patients with metastatic colorectal cancer in the controlled phase III clinical trial (SUNLIGHT).
The most common adverse drug reactions (≥ 30%) are neutropenia (69% [48% ≥ Grade 3]), fatigue (35% [3% ≥ Grade 3]), and nausea (33% [1% ≥ Grade 3]).
The most common adverse drug reactions (≥ 2%) that resulted in treatment discontinuation, dose reduction, dose delay, or dose interruption of LONSURF when used in combination with bevacizumab were neutropenia, fatigue, thrombocytopenia, nausea and anaemia.
When LONSURF was used in combination with bevacizumab, the frequency of the following adverse drug reactions was increased compared to LONSURF as monotherapy: neutropenia (69% vs 53%), severe neutropenia (48% vs 34%), thrombocytopenia (24% vs 16%), stomatitis (11% vs 6%).

Tabulated list of adverse reactions

The adverse drug reactions observed from the 533 treated patients with metastatic colorectal cancer, in the placebo-controlled Phase III (RECOURSE) clinical trial and 335 patients with metastatic gastric cancer treated in the placebo-controlled Phase III (TAGS) clinical trial, 246 patients treated with LONSURF monotherapy and 246 patients treated with LONSURF in combination with bevacizumab for metastatic colorectal cancer in the controlled Phase III (SUNLIGHT) clinical trial are shown in Tables 6 and 7. They are classified according to System Organ Class (SOC) and the appropriate Medical Dictionary for Regulatory (MedDRA) term is used to describe the drug reaction and its synonyms and related conditions.

Adverse reactions known to occur with LONSURF 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 Drug Reactions (ADRs) reported very commonly (i.e. ≥ 10 % of patients) in patients treated with LONSURF in RECOURSE and TAGS, and SUNLIGHT studies are listed in Table 6 and 7 respectively, presented by grade (all grades and ≥ Grade 3).

Table 6: Very common Adverse Drug Reactions (ADRs) Reported in Patients treated with LONSURF in RECOURSE and TAGS Trials

System Organ Class (MedDRA)[a] Preferred Term	LONSURF (N=868) %		Placebo (N=433) %	
	All Grades	≥ Grade 3	All Grades	≥ Grade 3
Blood And Lymphatic System Disorders				
Anaemia	31.8	12.1	6.2	2.3
Leukopenia	27.4	10.8	0.9	0
Neutropenia	52.9	34.1	1.8	0
Thrombocytopenia	18.1	3.7	2.5	0.2
Gastrointestinal Disorders				
Diarrhoea	20.7	2.4	9.2	0.5
Nausea	34.0	1.4	12.7	0.5
Vomiting	16.5	0.6	5.5	0.5
General Disorders And Administration Site Conditions				

System Organ Class (MedDRA)[a] Preferred Term	LONSURF (N=868) % All Grades	≥ Grade 3	Placebo (N=433) % All Grades	≥ Grade 3
Fatigue	32.1	3.8	15.9	2.5
Metabolism And Nutrition Disorders				
Decreased Appetite	23.3	2.2	11.3	0.7

a. Different MedDRA preferred terms that were considered clinically similar have been grouped into a single term.

Table 7: Very common Adverse Drug Reactions (ADRs) Reported in Patients treated with LONSURF in the SUNLIGHT Trial

System Organ Class (MedDRA)[a] Preferred Term	LONSURF (N=246) % All Grades	≥ Grade 3	LONSURF + BEVACIZUMAB (N=246) % All Grades	≥ Grade 3
Blood and lymphatic system disorders				
Neutropenia	132 (53.7)	82 (33.3)	170 (69.1)	118 (48.0)
Anaemia	62 (25.2)	20 (8.1)	62 (25.2)	15 (6.1)
Thrombocytopenia	25 (10.2)	1 (0.4)	58 (23.6)	8 (3.3)
Gastrointestinal disorders				
Nausea	51 (20.7)	3 (1.2)	82 (33.3)	3 (1.2)
Vomiting	27 (11.0)	3 (1.2)	41 (16.7)	2 (0.8)
Diarrhoea	38 (15.4)	5 (2.0)	38 (15.4)	1 (0.4)
Stomatitis	10 (4.1)	-	27 (11.0)	1 (0.4)
General disorders and administration site conditions				
Fatigue	64 (26.0)	8 (3.3)	86 (35.0)	8 (3.3)
Metabolism and nutrition disorders				
Decreased appetite	18 (7.3)	-	30 (12.2)	1 (0.4)

ADRs reported with a frequency < 10 % in patients treated with LONSURF from the RECOURSE and TAGS, and SUNLIGHT studies are listed in Table 8 and 9 respectively below by MedDRA system organ class and by frequency: common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare ((≥ 1/10000 to < 1/1000). Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness.

Table 8: Adverse Drug Reactions (ADRs) Reported In Clinical Trials In < 10 % Of Patients Treated With LONSURF in RECOURSE and TAGS Trials

System Organ Class (MedDRA)[a] Preferred Term	Common	Uncommon
Infections and infestations	– Lower respiratory tract infection	– Septic shock[b] – Enteritis infectious – Lung infection – Biliary tract infection – Influenza – Urinary tract infection – GingivitisHerpes zoster – Tinea pedis – Candida infection – Bacterial infection – Infection – Upper respiratory tract infection – Conjunctivitis
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)		– Cancer pain
Blood and lymphatic system disorders	– Febrile neutropenia – Lymphopenia	– Pancytopenia – Granulocytopenia – Monocytopenia – Erythropenia – Leukocytosis – Monocytosis
Metabolism and nutrition disorders	– Hypoalbuminaemia	– Dehydration – Hyperglycaemia – Hyperkalaemia – Hypokalaemia – Hypophosphataemia – Hypernatraemia – Hyponatraemia – Hypocalcaemia – Gout
Psychiatric disorders		– Anxiety – Insomnia
Nervous system disorders	– Dysgeusia – Neuropathy peripheral	– Neurotoxicity – Dysaesthesia – Hyperaesthesia – Hypoaesthesia – Syncope – Paraesthesia – Burning sensation – Lethargy – Dizziness – Headache

System Organ Class (MedDRA)[a] Preferred Term	Common	Uncommon
Eye disorders		– Visual acuity reduced – Vision blurred – Diplopia – Cataract – Dry eye
Ear and labyrinth disorders		– Vertigo – Ear discomfort
Cardiac disorders		– Angina pectoris – Arrhythmia – Palpitations
Vascular disorders		– Embolism – Hypertension – Hypotension – Flushing
Respiratory, thoracic and mediastinal disorders	– Dyspnoea	– Pulmonary embolism – Pleural effusion – Rhinorrhoea – Dysphonia – Oropharyngeal pain – Epistaxis – Cough

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

System Organ Class (MedDRA)[a] Preferred Term	Common	Uncommon
Renal and urinary disorders	– Proteinuria	– Renal failure – Cystitis noninfective – Micturition disorder – Haematuria – Leukocyturia
Reproductive system and breast disorders		– Menstrual disorder
General disorders and administration site conditions	– Pyrexia – Oedema – Mucosal inflammation – Malaise	– General physical health deterioration – Pain – Feeling of body temperature change – Xerosis – Discomfort
Investigations	– Hepatic enzyme increased – Blood alkaline phosphatase increased – Weight decreased	– Blood creatinine increased – Electrocardiogram QT prolonged – International normalised ratio increased – Activated partial thromboplastin time prolonged – Blood urea increased – Blood lactate dehydrogenase increased – Protein total decreased – C-reactive protein increased – Haematocrit decreased

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.

Rare and very rare events reported in the RECOURSE and TAGS Phase III clinical trials could not be estimated from the available data due to the limited number of patients exposed to LONSURF.

Table 9: Adverse Drug Reactions (ADRs) Reported In Clinical Trials In < 10 % Of Patients Treated with LONSURF in the SUNLIGHT Trial

System Organ Class (MedDRA)[a] Preferred Terms	Frequency	
	LONSURF	LONSURF + BEVACIZUMAB
Infections and infestations		
Bacterial infection	Uncommon	-
Infection	Uncommon	Common
Oral herpes	Uncommon	Uncommon
Candida infection	Uncommon	-

System Organ Class (MedDRA)[a] Preferred Terms	Frequency	
	LONSURF	**LONSURF + BEVACIZUMAB**
Lower respiratory tract infection	Uncommon	-
Gingivitis	-	Uncommon
Urinary tract infection	-	Uncommon
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Oncologic complication	-	Uncommon
Blood and lymphatic system disorders		
Leukopenia	Common	Common
Lymphopenia	Common	Common
Febrile neutropenia	Common	Uncommon
Leukocytosis	Uncommon	-
Pancytopenia	-	Uncommon
Metabolism and nutrition disorders		
Hypoalbuminaemia	Uncommon	Uncommon
Dehydration	Uncommon	-
Hyperuricaemia	Uncommon	Uncommon
Hyperkalaemia	Uncommon	-
Hypokalaemia	Uncommon	-
Hypomagnesaemia	Uncommon	-
Hyponatraemia	Uncommon	-
Hypercalcaemia	-	Uncommon
Hyperglycaemia	-	Uncommon
Nervous system disorders		
Headache	Uncommon	Common
Dizziness	Uncommon	Common
Dysgeusia	Uncommon	Common
Paraesthesia	Uncommon	Uncommon
Ataxia	Uncommon	-
Neurotoxicity	Uncommon	-
Somnolence	Uncommon	-
Neuralgia	-	Uncommon
Neuropathy peripheral	-	Uncommon
Eye disorders		
Eye irritation	-	Uncommon
Lacrimal gland enlargement	-	Uncommon
Ear and labyrinth disorders		
Tinnitus	-	Uncommon

System Organ Class (MedDRA)[a] Preferred Terms	Frequency	
	LONSURF	LONSURF + BEVACIZUMAB
Vascular disorders		
Hypertension	-	Common
Respiratory, thoracic and mediastinal disorders		
Hiccups	Uncommon	Uncommon
Cough	Uncommon	-
Dyspnoea	-	Common
Dysphonia	-	Uncommon
Rhinorrhoea	-	Uncommon
Gastrointestinal disorders		
Constipation	Common	Common
Abdominal pain	Common	Common
Dyspepsia	Common	Uncommon
Epigastric discomfort	Uncommon	-
Gastritis	Uncommon	-
Oral disorder	Uncommon	Common
Abdominal distension	Uncommon	Uncommon
Colitis	Uncommon	Uncommon
Abdominal discomfort	Uncommon	-
Intestinal obstruction	Uncommon	-
Retching	Uncommon	-
Small intestinal obstruction	Uncommon	-
Mouth ulceration	-	Common
Gastrointestinal disorder	-	Uncommon
Anal inflammation	-	Uncommon
Flatulence	-	Uncommon
Gingival pain	-	Uncommon
Oesophageal pain	-	Uncommon
Salivary gland enlargement	-	Uncommon
Hepatobiliary disorders		
Hyperbilirubinaemia	Common	Common
Hepatotoxicity	Uncommon	-
Cholestasis	Uncommon	-
Skin and subcutaneous tissue disorders		
Alopecia	Common	Common
Rash	Common	Uncommon
Dry skin	Uncommon	Common

System Organ Class (MedDRA)[a] Preferred Terms	Frequency	
	LONSURF	LONSURF + BEVACIZUMAB
Pruritus	Uncommon	Uncommon
Skin toxicity	Uncommon	-
Nail disorder	-	Uncommon
Palmar-plantar erythrodysaesthesia syndrome[b]	-	Uncommon
Musculoskeletal and connective tissue disorders		
Muscular weakness	Uncommon	Uncommon
Pain in extremity	Uncommon	Uncommon
Musculoskeletal pain	Uncommon	-
Arthralgia	-	Common
Myalgia	-	Common
Renal and urinary disorders		
Renal failure	Uncommon	-
Proteinuria	-	Uncommon
Reproductive system and breast disorders		
Menstrual disorder	-	Uncommon
General disorders and administration site conditions		
Pyrexia	Common	Uncommon
Mucosal inflammation	Uncommon	Uncommon
Pain	Uncommon	Uncommon
Feeling of body temperature change	Uncommon	-
General physical health deterioration	Uncommon	-
Discomfort	-	Uncommon
Investigations		
Hepatic enzyme increased	Common	Common
Weight decreased	Common	Common
Blood alkaline phosphatase increased	Uncommon	Uncommon
Blood creatinine increased	Uncommon	-
C-reactive protein increased	Uncommon	-
Troponin T increased	Uncommon	-

[a] Different MedDRA preferred terms that were considered clinically similar have been grouped into a single term; [b] Hand-foot skin reaction; Treatment-related EAE include sponsor upgrade

Elderly

Patients aged ≥ 65 years who received LONSURF as monotherapy had a higher incidence (≥ 5%) of the following treatment-related adverse events compared to patients aged < 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 LONSURF was used in combination with bevacizumab (SUNLIGHT trial), 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 Phase III placebo-controlled clinical trials, treatment-related infections occurred more frequently in LONSURF-treated patients (5.8 %) compared to those receiving placebo (1.8 %). When LONSURF was used in combination with bevacizumab (SUNLIGHT trial), treatment-related infections occurred similarly in patients who received LONSURF with bevacizumab (2.8%) compared to LONSURF-treated patients (2.4%).

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 LONSURF-treated patients who received prior radiotherapy compared to those that did not. When LONSURF was used in combination with bevacizumab (SUNLIGHT trial), 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: LONSURF with bevacizumab (73.7% versus 77.4%) and in LONSURF -treated patients (64.7% versus 67.7%).

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

There have been reports of interstitial lung disease in patients receiving LONSURF post approval.

4.9 OVERDOSE

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia)

The highest dose of LONSURF administered was 180 mg/m^2 per day. The adverse events reported in association with an overdose 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 LONSURF.

If overdose occurs, supportive management is recommended.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: antineoplastic agents, antimetabolites. ATC code: L01BC59

Mechanism of action

LONSURF 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 thymidine phosphorylase (TPase) and readily metabolised by a first-pass effect following oral administration, hence the inclusion of the thymidine phosphorylase inhibitor, tipiracil hydrochloride.

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

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

Pre-clinical data

Toxicology assessment of tipiracil hydrochloride/trifluridine 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, anaemia, bone marrow hypoplasia, atrophic changes in the lymphatic and hematopoietic tissues and the gastrointestinal tract, were reversible within nine weeks of medicine withdrawal. Whitening, breakage, and malocclusion (degeneration and disarrangement in the ameloblasts, papillary layer cells and odontoblasts) were observed in teeth of rats treated with trifluridine/ tipiracil hydrochloride, which are considered rodent specific and not relevant in humans.

Clinical Trials

Metastatic colorectal cancer

The clinical efficacy and safety of LONSURF were evaluated in an international, randomized, 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 randomized 2:1 to receive LONSURF (N=534) plus best supportive care (BSC) or matching placebo (N=266) plus BSC. LONSURF dosing was based on body surface area (BSA) with a starting dose of 35 mg/m^2/dose. Study treatment was administered orally twice daily after morning and evening meals for five days a week with a two-day rest for two weeks, followed by a 14-day rest, repeated every four weeks. Patients continued therapy until disease progression or unacceptable toxicity (see *section - 4.2 Dose And Method of Administration*).

Of the 800 randomized patients, the median age was 63 years, 61 % were male, 58 % and 35 % were Caucasian and Asian respectively, and 1 % were African American. All patients had baseline Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of zero or one. The primary site of disease was the colon (62 %) or the 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 three. All patients received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy. All but one patient received bevacizumab, and all but two patients with KRAS wild type tumours received panitumumab or cetuximab. The two treatment groups were comparable with respect to demographic and baseline disease characteristics.

Treatment with LONSURF plus BSC resulted in a clinically meaningful and statistically significant improvement in overall survival in comparison to placebo plus BSC (see Table 10 and Figure 1).

Table 10: Efficacy Results (Intent-To-Treat Population) From The Phase III (RECOURSE) Clinical Trial In Patients With Metastatic Colorectal Cancer

	LONSURF plus BSC (N=534)	**Placebo plus BSC (N=266)**
Overall Survival (in ITT population)		
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 (in ITT population)		
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]	
	LONSURF plus BSC (N=534)	**Placebo plus BSC (N=266)**
P-value[c]	<0.0001 (1-sided and 2-sided)	
Number of patients progression-free (%)[a] [95 % CI][d] (in ITT population)		
At 2 months	(47.3) [42.9, 51.5]	(20.8) [16.0, 26.0]
At 4 months	(25.0) [21.3, 28.8]	(4.7) [2.5, 7.9]
At 6 months	(15.1) [12.1, 18.5]	(1.4) [0.4, 3.7]
At 8 months	(8.0) [5.7, 10.8]	(1.4) [0.4, 3.7]

[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) [d] Using log-log transformation methodology of Kalbfleisch and Prentice

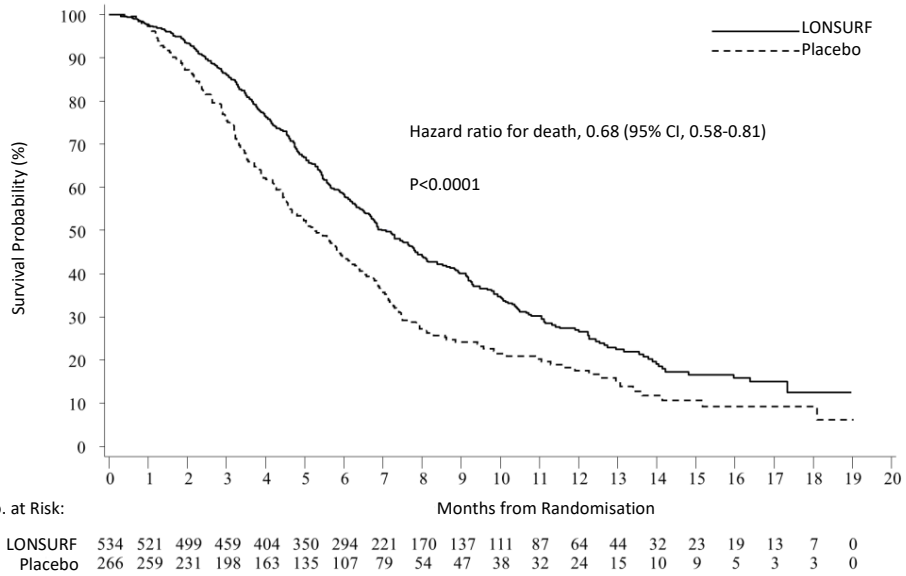
An updated OS analysis, carried out at 89 % (N = 712) of events, confirmed the clinically meaningful and statistically significant survival benefit of LONSURF plus BSC compared to placebo plus BSC (hazard ratio: 0.69; 95 % CI [0.59 to 0.81]; p < 0.0001). The median OS was 7.2 months in the LONSURF plus BSC arm vs 5.2 months in the placebo plus BSC arm, with one year survival Kaplan-Meier estimates of 27.1 % and 16.6 %, respectively.

Table 11: Efficacy Results (Tumour-Response (TR) Population) From The Phase III (RECOURSE) Clinical Trial In Patients With Metastatic Colorectal Cancer

	LONSURF plus BSC (N=502)	Placebo plus BSC (N=258)
Overall Response Rate and Disease Control Rate (TR population)		
ORR (Complete or partial), n (%) [95 % CI][e]	8 (1.6) [0.7, 3.1]	1 (0.4) [0.0, 2.1]
P-value[f]	0.2862	
DCR (complete, partial or stable disease), n (%) [95% CI]	221 (44.0) [39.6, 48.5]	42 (16.3) [12.0, 21.4]
P-value[f]	<0.0001	

[e] Exact 2-sided confidence interval based on Clopper-Pearson methodology [f] Fisher's Exact test (2-sided)

Figure 1- Kaplan-Meier Curves Of Overall Survival (Intent-To-Treat Population) In Patients With Metastatic Colorectal Cancer (RECOURSE)



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Sixty one percent (61 %) n=455 of all randomized patients received a fluoropyrimidine as part of their last treatment regimen prior to randomization, of which 455 (94 %) were refractory to the fluoropyrimidine at that time. Among these patients, OS benefit with LONSURF remained favourable (HR=0.75, 95 % CI 0.59 to 0.94).

Treatment with LONSURF 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 LONSURF group and placebo group was 5.7 months and 4.0 months, respectively, with a hazard ratio (HR) of 0.66 (95 % CI: 0.56, 0.78), p < 0.0001.

The safety and efficacy of LONSURF in combination with bevacizumab compared to LONSURF monotherapy, was evaluated in an international, randomised, open-label, phase III study (SUNLIGHT). Patients in the SUNLIGHT trial had metastatic colorectal cancer and 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). The frequency of some adverse reactions was increased when LONSURF was used in combination with bevacizumab compared to LONSURF monotherapy (see *section 4.8 - Adverse Effects (Undesirable Effects)*).

Metastatic gastric cancer

The clinical efficacy and safety of LONSURF 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 every eight weeks.

In total, 507 patients were randomised 2:1 to receive LONSURF (N = 337) plus best supportive care (BSC) or placebo (N = 170) plus BSC. LONSURF 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 five days a week with two day rest for two weeks, followed by 14 days of rest, repeated every four weeks. Patients continued treatment until disease progression or unacceptable toxicity (see *section 4.2 - Dose And Method of Administration*).

Of the 507 randomised patients, the median age was 63 years, 73 % were male, 70 % and 16 % were Caucasian and Asian respectively, and <1 % were African American. All patients had baseline Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of zero or one. Primary cancer was gastric (71.0 %) or gastroesophageal junction cancer (28.6 %), or both (0.4 %). The median number of prior treatment regimens for metastatic disease was three. Nearly all patients (99.8 %) received prior treatment with fluoropyrimidine, all patients received prior treatment with platinum, and 90.5 % received prior treatment with taxane. Approximately half of patients (55.4 %) received prior treatment with irinotecan, and 33.3 % with ramucirumab. The two 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 LONSURF plus BSC resulted in a statistically significant and clinically meaningful improvement in OS compared to placebo plus BSC. The hazard ratio (HR) was 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 LONSURF group. The median OS was 5.7 months (95 % CI: 4.8, 6.2) for the LONSURF group versus 3.6 months (95 % CI: 3.1, 4.1) for the placebo group; with one year survival rates of 21.2 % and 13.0 %, respectively.

PFS was significantly improved in patients receiving LONSURF plus BSC compared to placebo plus BSC (HR of 0.57; 95 % CI [0.47 to 0.70]; p < 0.0001 (see Table 12, Figures 2 and 3); with PFS rates at two, four and six months in favour of the LONSURF arm.

Table 12 - Efficacy Results From The Phase III (TAGS) Clinical Trial In Patients With Metastatic Gastric Cancer

	LONSURF 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)	
3-month OS rate (%) [95 % CI]	72.4 [67.3, 76.9]	60.3 [52.4, 67.2]
6-month OS rate (%) [95% CI]	46.7 [41.1, 52.2]	33.1 [25.9, 40.3]
9-month OS rate (%) [95 % CI]	30.3 [24.9, 35.8]	23.3 [16.8, 30.3]
12-month OS rate (%) [95 % CI]	21.2 [16.1, 26.7]	13.0 [7.7, 19.8]
Progression-Free Survival		
Number of Progressions 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)	
2-month PFS rate (%) [95 % CI]	49.7 [44.1, 55.1]	25.3 [18.9, 32.1]
4-month PFS rate (%) [95 % CI]	26.8 [21.9, 31.9]	7.7 [4.2, 12.5]
6-month PFS rate (%) [95 % CI]	14.6 [10.7, 19.0]	6.4 [3.2, 10.9]

[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 2- Kaplan-Meier Curves Of Overall Survival In Patients With Metastatic Gastric Cancer (TAGS)

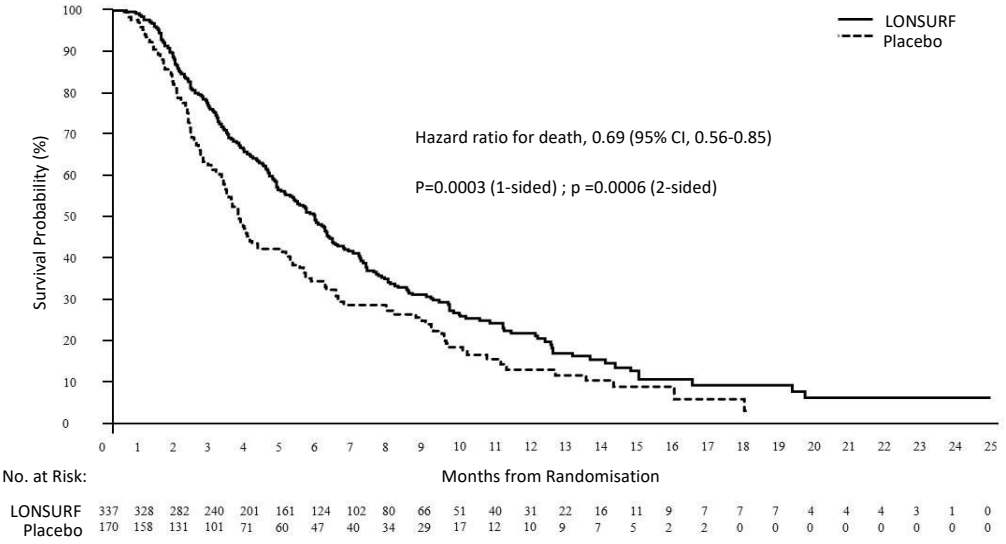
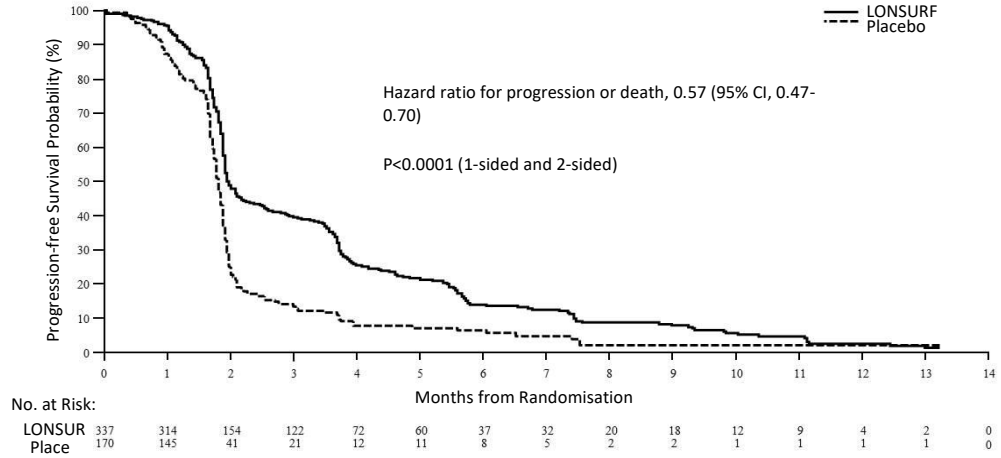


Figure 3 - Kaplan-Meier Curves Of Progression-Free Survival In Patients With Metastatic Gastric Cancer (TAGS)



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, geographic region (Japan; ex-Japan), ECOG PS, prior ramucirumab treatment, prior irinotecan treatment, number of prior regimens (2; 3; ≥ 4), time since metastatic diagnosis (< 24; ≥ 24 months), previous gastrectomy, primary tumour site (gastric; gastroesophageal junction), number of metastatic sites (<3; ≥ 3) and HER2 status.

Patients who had received prior ramucirumab (as monotherapy or in combination) treatment had a median OS in the LONSURF and placebo arms of 5.0 months and 3.8 months respectively (HR = 0.76; 95 % CI: 0.529, 1.086). Median OS for patients who had not received prior ramucirumab treatment in the LONSURF and placebo arms, was 6.0 months and 3.3 months respectively (HR = 0.66; 95 % CI: 0.506, 0.855).

Patients who had received prior irinotecan treatment had a median OS in the LONSURF and placebo arms of 5.1 months and 3.6 months respectively (HR = 0.87; 95 % CI: 0.658, 1.147). Median OS for patients who had not received prior irinotecan treatment in the LONSURF and placebo arms was 6.1 months and 3.3 months respectively (HR = 0.55; 95 % CI: 0.390, 0.762).

The DCR (complete response or partial response or stable disease) was significantly higher in patients treated with LONSURF (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 LONSURF group versus 2.3 months for the placebo group with HR of 0.69 (95 % CI: 0.562, 0.854), p-value = 0.0005.

Quality of life remained stable in both treatment groups, with no clinically relevant changes from baseline, indicating that QoL was maintained during treatment with LONSURF.

Elderly

There is limited data in LONSURF treated patients aged between 75 and 84 years (N=85) in the RECOURSE and TAGS studies. There were no patients aged ≥ 85 years in the RECOURSE study, and

only two in the TAGS study. The effect of LONSURF on overall survival was similar in patients aged <65 years and ≥65 years.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

After oral administration of LONSURF 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 LONSURF 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 LONSURF (35 mg/m²) 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 LONSURF (35 mg/m^2/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 LONSURF 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 LONSURF. Following multiple doses of LONSURF (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 LONSURF (35 mg/m²/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/ m²/dose).

Effect of food

When LONSURF at a single dose of 35 mg/m² 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 Cmax, tipiracil hydrochloride Cmax and AUC decreased by approximately 40 % compared to those in a fasting state. In clinical studies LONSURF was administered within 1 hour after completion of the morning and evening meals (see *section - 4.2 Dose And Method of Administration*).

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 LONSURF (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.

Metabolism

Trifluridine was mainly eliminated by metabolism via TPase to form an inactive metabolite, FTY. 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.

Excretion

Following the multiple-dose administration of LONSURF 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 LONSURF (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 LONSURF 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 LONSURF with [^{14}C]-tipiracil hydrochloride, recovered radioactivity was 77 % of the dose, which consisted of 27 % urinary excretion and 50 % faecal excretion.

In a dose finding study (15 to 35 mg/ m^2 BID), the $AUC_{0\text{-}10}$ 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 pharmacokinetic analysis, there is no clinically relevant effect of age, gender or race on the pharmacokinetics of trifluridine or tipiracil hydrochloride.

Renal impairment

Of the 533 patients in the RECOURSE study who received LONSURF, 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 LONSURF 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 LONSURF 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).
All patients received LONSURF 35 mg/m2 twice daily except for patients with severe renal impairment who 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).

Mild renal impairment had no important effect on steady-state AUC0-last of trifluridine and tipiracil. Moderate renal impairment increased steady-state AUC0-last of trifluridine by 56% and tipiracil by 139% compared to normal renal function. Severe renal impairment increased the steady-state AUC0-last of trifluridine by 37% and tipiracil by 308% compared to normal renal function.

The PK of trifluridine and tipiracil hydrochloride have not been studied in patients with end-stage renal disease (CrCl <15 mL/min or requiring dialysis) (*see section 4.2 Dose And Method of Administration* and *section - 4.4 Special Warnings and Precautions for Use*).

Hepatic impairment

Based on the population pharmacokinetic analysis, liver function parameters including alkaline phosphatase (ALP, 36-2,322 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 pharmacokinetics 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 Cancer Institute [NCI] Criteria Group B and C, respectively) and in patients with normal hepatic function, no clinically important differences in the mean exposure were observed. 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. Five out of six patients with moderate hepatic impairment and 2 out of 8 patients in the control group experienced Grade 3 or 4 increased bilirubin levels. 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. Enrolment into the dedicated hepatic impairment study was discontinued due to the high incidence of Grade 3 or 4 increased bilirubin levels in patients with moderate hepatic impairment. There is no need for a starting dose adjustment in patients with mild hepatic impairment (see *section - 4.2 Dose and Method of Administration*). The use of LONSURF is not recommended in patients with baseline moderate or

severe hepatic impairment due to the observed high incidence of Grade 3 or 4 hyperbilirubinaemia in patients with baseline moderate hepatic impairment (see *section - 4.4 Special Warnings and Precautions for Use*).

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. Tipiracil hydrochloride has been identified as both a substrate for, and inhibitor of 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 LONSURF is administered concomitantly with inhibitors of OCT2 and MATE1.

Pharmacokinetic/pharmacodynamic relationship

The efficacy and safety of LONSURF in mCRC 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

Genotoxicity

Trifluridine is mutagenic and clastogenic. It induced gene mutation in bacteria and chromosome aberration in Chinese hamster ovary cells in vitro and in mouse micronucleus test in vivo. Tipiracil hydrochloride was not genotoxic in these genotoxicity assays.

Carcinogenicity

No long-term studies evaluating the carcinogenic potential of trifluridine/tipiracil in animals have been performed. Based on the pharmacological activity and genotoxicity of trifluridine, trifluridine is expected to be carcinogenic.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

- Lactose monohydrate
- Pre-gelatinised starch
- Stearic acid

Film-coating:
- Titanium dioxide
- Hypromellose
- Macrogol (8000)
- Magnesium stearate
- Iron oxide red (E172) (specific to LONSURF 20/8.19)

Ink imprinting:
- Indigo carmine aluminium lake (E132)
- Iron oxide yellow (E172)
- Iron oxide red (E172)
- Shellac
- Carnauba wax
- Talc
- Titanium dioxide (E171)

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

36 months.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

Nature and contents of container

Tablets are supplied in a box containing aluminium / aluminium blister trays and a laminated desiccant. Each blister tray contains ten tablets. Pack size of 20 and 60[#] film-coated tablets.

6.5 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

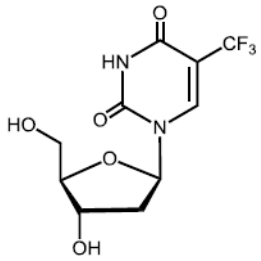
6.6 PHYSICOCHEMICAL PROPERTIES

6.6.1 Chemical structure

Trifluridine

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.

Chemical structure:



Molecular formula:

$C_{10}H_{11}F_3N_2O_5$ (Relative Molecular Mass: 296.20)

CAS number

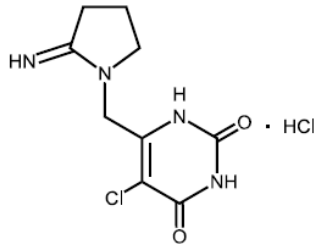
70-00-8

Tipiracil

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.

[#] The 60 tablet pack size is not distributed in Australia

Chemical structure:



Molecular formula:

$C_9H_{11}ClN_4O_2$.HCl (Relative Molecular Mass: 279.12)

CAS number

183204-72-0

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4: Prescription-only Medicine

8 SPONSOR

Servier Laboratories (Aust.) Pty. Ltd.
www.servier.com.au
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Burnley, 3121, Victoria, Australia

9 DATE OF FIRST APPROVAL

23 May 2017

10 DATE OF REVISION

05 November 2024

SUMMARY TABLE OF CHANGES

Section(s) Changed	Summary of new information
4.4, 4.6, 4.8, 5.1	Safety-related update