

**ANNEX I**  
**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

Lonsurf 15 mg/6.14 mg film-coated tablets

Lonsurf 20 mg/8.19 mg film-coated tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

### Lonsurf 15 mg/6.14 mg film-coated tablets

Each film-coated tablet contains 15 mg trifluridine and 6.14 mg tipiracil (as hydrochloride).

### Excipient with known effect

Each film-coated tablet contains 90.735 mg of lactose monohydrate.

### Lonsurf 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).

### Lonsurf 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.

### Lonsurf 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

Lonsurf 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.

Lonsurf 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

Lonsurf 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

Lonsurf should be prescribed by physicians experienced in the administration of anticancer therapy.

### Posology

The recommended starting dose of Lonsurf in adults, as monotherapy or in combination with bevacizumab, is 35 mg/m<sup>2</sup>/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 Lonsurf 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 <sup>2</sup> )	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 <sup>2</sup>	< 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<sup>2</sup> 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**

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

<sup>a</sup> 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**

<b>Adverse reaction</b>	<b>Recommended dose modifications</b>
<ul style="list-style-type: none"> <li>• Febrile neutropenia</li> <li>• CTCAE* Grade 4 neutropenia (<math>&lt; 0.5 \times 10^9/L</math>) or thrombocytopenia (<math>&lt; 25 \times 10^9/L</math>) that results in more than 1 week's delay in start of next cycle</li> <li>• 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</li> </ul>	<ul style="list-style-type: none"> <li>• Interrupt dosing until toxicity resolves to Grade 1 or baseline.</li> <li>• When resuming dosing, decrease the dose level by 5 mg/m<sup>2</sup>/dose from the previous dose level (Table 4).</li> <li>• Dose reductions are permitted to a minimum dose of 20 mg/m<sup>2</sup>/dose twice daily (or 15 mg/m<sup>2</sup>/dose twice daily in severe renal impairment).</li> <li>• Do not increase dose after it has been reduced.</li> </ul>

\* Common terminology criteria for adverse events

**Table 4 - Dose reductions according to BSA**

Reduced dose	BSA (m <sup>2</sup> )	Dose in mg (2x daily)	Tablets per dose (2x daily)		Total daily dose (mg)
			15 mg/6.14 mg	20 mg/8.19 mg	
<b>Level 1 dose reduction: From 35 mg/m<sup>2</sup> to 30 mg/m<sup>2</sup></b>					
<b>30 mg/m<sup>2</sup></b>	< 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
<b>Level 2 dose reduction: From 30 mg/m<sup>2</sup> to 25 mg/m<sup>2</sup></b>					
<b>25 mg/m<sup>2</sup></b>	< 1.10	25 <sup>a</sup>	2 <sup>a</sup>	1 <sup>a</sup>	50 <sup>a</sup>
	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
<b>Level 3 dose reduction: From 25 mg/m<sup>2</sup> to 20 mg/m<sup>2</sup></b>					
<b>20 mg/m<sup>2</sup></b>	< 1.14	20	0	1	40
	1.14 – 1.34	25 <sup>a</sup>	2 <sup>a</sup>	1 <sup>a</sup>	50 <sup>a</sup>
	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

<sup>a</sup> 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<sup>2</sup> twice daily is recommended (see sections 4.4 and 5.2). One dose reduction to a minimum dose of 15 mg/m<sup>2</sup> 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 <sup>2</sup> )	Dose in mg (2x daily)	Tablets per dose (2x daily)		Total daily dose (mg)
			15 mg/6.14 mg	20 mg/8.19 mg	
<b>Starting dose</b>					
<b>20 mg/m<sup>2</sup></b>	< 1.14	20	0	1	40
	1.14 – 1.34	25 <sup>a</sup>	2 <sup>a</sup>	1 <sup>a</sup>	50 <sup>a</sup>
	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
<b>Dose reduction: From 20 mg/m<sup>2</sup> to 15 mg/m<sup>2</sup></b>					
<b>15 mg/m<sup>2</sup></b>	< 1.15	15	1	0	30
	1.15 – 1.49	20	0	1	40
	1.50 – 1.84	25 <sup>a</sup>	2 <sup>a</sup>	1 <sup>a</sup>	50 <sup>a</sup>
	1.85 – 2.09	30	2	0	60
	2.10 – 2.34	35	1	1	70
	≥ 2.35	40	0	2	80

<sup>a</sup> 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 Lonsurf 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 Lonsurf 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

Lonsurf 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

Lonsurf 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  $< 1.5 \times 10^9/L$ , if the platelet counts are  $< 75 \times 10^9/L$ , 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 Lonsurf (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 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, 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

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

The global incidence of adverse events (AEs) is similar in normal renal function ( $\text{CrCl} \geq 90 \text{ mL/min}$ ), mild ( $\text{CrCl} = 60 \text{ to } 89 \text{ mL/min}$ ) or moderate ( $\text{CrCl} = 30 \text{ to } 59 \text{ mL/min}$ ) 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 ( $\text{CrCl} = 15 \text{ to } 29 \text{ mL/min}$ ) and adjusted starting dose of  $20 \text{ mg/m}^2$  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 sections 4.2 and 5.2).

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

### 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  $> 1.5 \times \text{ULN}$ ), 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

Lonsurf 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 Lonsurf 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 Lonsurf, 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 Lonsurf 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 Lonsurf and for up to 6 months after ending treatment. Therefore, women of child-bearing potential must use highly effective contraceptive measures while taking Lonsurf and for 6 months after stopping treatment. 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.

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 Lonsurf 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). Lonsurf should not be used during pregnancy unless the clinical condition of the woman requires treatment with Lonsurf.

## Breast-feeding

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 (see section 5.3). A risk to the suckling child cannot be excluded. Breast-feeding should be discontinued during treatment with Lonsurf.

## Fertility

There are no data available on the effects of Lonsurf on human fertility. Results of animal studies did not indicate an effect of Lonsurf 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 Lonsurf treatment.

## **4.7 Effects on ability to drive and use machines**

Lonsurf 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 Lonsurf are bone marrow suppression and gastrointestinal toxicity (see section 4.4).

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

### 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 study (SUNLIGHT).

The most common adverse reactions ( $\geq 30\%$ ) are neutropenia (69% [48%  $\geq$  Grade 3]), fatigue (35% [3%  $\geq$  Grade 3]), and nausea (33% [1%  $\geq$  Grade 3]).

The most common adverse reactions ( $\geq 2\%$ ) 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 is used in combination with bevacizumab, the frequency of the following adverse 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 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 Lonsurf in monotherapy and the 246 patients treated with Lonsurf 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 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 reactions are grouped according to their frequencies. Frequency groups are defined by the following convention: very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1\ 000$  to  $< 1/100$ ); and rare ( $\geq 1/10\ 000$  to  $< 1/1\ 000$ ).

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

**Table 6 - Adverse reactions reported in clinical studies in patients treated with Lonsurf**

System Organ Class (MedDRA) <sup>a</sup>	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 <sup>b</sup>	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

System Organ Class (MedDRA) <sup>a</sup>	Adverse reactions	Frequency	
		Monotherapy	Combination with bevacizumab
	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	Decreased appetite	Very common	Very common
	Hypoalbuminaemia	Common	Uncommon
	Dehydration	Uncommon	-
	Hyperglycaemia	Uncommon	Uncommon
	Hyperkalaemia	Uncommon	-
	Hypocalcaemia	Uncommon	-
	Hypokalaemia	Uncommon	-
	Hyponatraemia	Uncommon	-
	Hypophosphataemia	Uncommon	-
	Gout	Rare	-
	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 <sup>b</sup>	Uncommon	-
	Dysphonia	Uncommon	Uncommon
	Cough	Uncommon	-
	Epistaxis	Uncommon	-

System Organ Class (MedDRA) <sup>a</sup>	Adverse reactions	Frequency	
		Monotherapy	Combination with bevacizumab
	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 erythrodysesthesia syndrome <sup>c</sup>	Uncommon	Uncommon
	Acne	Uncommon	-
	Hyperhidrosis	Uncommon	-
	Urticaria	Uncommon	-
	Blister	Rare	-
	Erythema	Rare	-
	Photosensitivity reaction	Rare	-
	Skin exfoliation	Rare	-

System Organ Class (MedDRA) <sup>a</sup>	Adverse reactions	Frequency	
		Monotherapy	Combination with bevacizumab
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 Lonsurf as monotherapy had a higher incidence ( $\geq 5\%$ ) 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 Lonsurf is used in combination with bevacizumab, patients 65 years of age or older had a higher incidence ( $\geq 5\%$ ) 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 Lonsurf-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 Lonsurf with bevacizumab (2.8%) compared to Lonsurf-treated patients (2.4%).

### Proteinuria

In the Phase III placebo-controlled clinical studies, treatment-related proteinuria occurred more frequently in Lonsurf-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 Lonsurf with bevacizumab (0.4%) reported a treatment-related proteinuria which was Grade 2 and none among the Lonsurf-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 RECURSE (54.6% versus 49.2%, respectively), of note febrile neutropenia was higher in Lonsurf-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: Lonsurf with bevacizumab (73.7% versus 77.4%) and in Lonsurf-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 Lonsurf 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 national reporting system listed in [Appendix V](#).

## **4.9 Overdose**

The highest dose of Lonsurf administered in clinical studies was 180 mg/m<sup>2</sup> 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 Lonsurf.

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

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 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

Lonsurf 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 Lonsurf as monotherapy versus placebo

The clinical efficacy and safety of Lonsurf 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 Lonsurf (N = 534) plus best supportive care (BSC) or matching placebo (N = 266) plus BSC. Lonsurf dosing was based on BSA with a starting dose of 35 mg/m<sup>2</sup>/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 Lonsurf 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 Lonsurf 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**

	<b>Lonsurf plus BSC (N=534)</b>	<b>Placebo plus BSC (N=266)</b>
<b>Overall survival</b>		
Number of deaths, N (%)	364 (68.2)	210 (78.9)
Median OS (months) <sup>a</sup> [95% CI] <sup>b</sup>	7.1 [6.5, 7.8]	5.3 [4.6, 6.0]
Hazard ratio [95% CI]	0.68 [0.58, 0.81]	
P-value <sup>c</sup>	< 0.0001 (1-sided and 2-sided)	
<b>Progression-Free Survival</b>		
Number of progression or death, N (%)	472 (88.4)	251 (94.4)
Median PFS (months) <sup>a</sup> [95% CI] <sup>b</sup>	2.0 [1.9, 2.1]	1.7 [1.7, 1.8]
Hazard ratio [95% CI]	0.48 [0.41, 0.57]	
P-value <sup>c</sup>	<0.0001 (1-sided and 2-sided)	

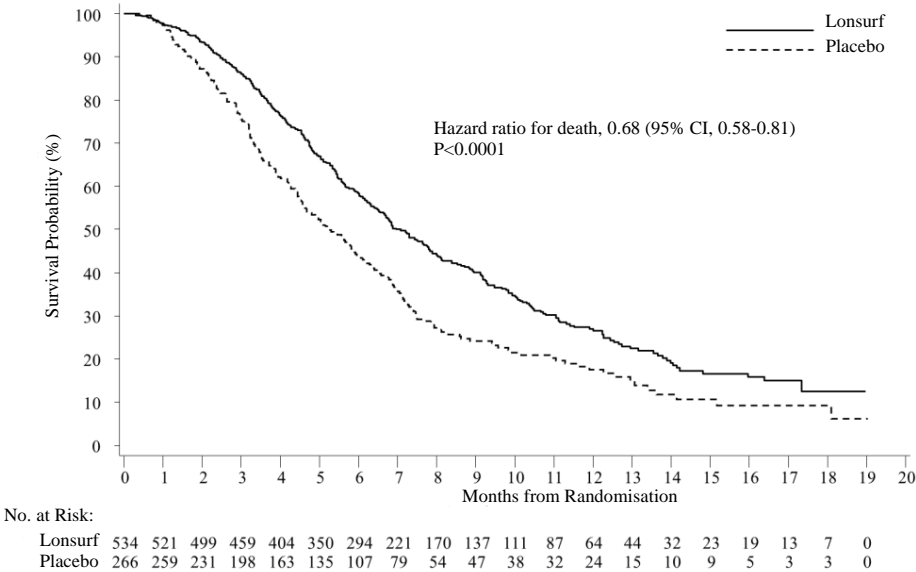
<sup>a</sup> Kaplan-Meier estimates

<sup>b</sup> Methodology of Brookmeyer and Crowley

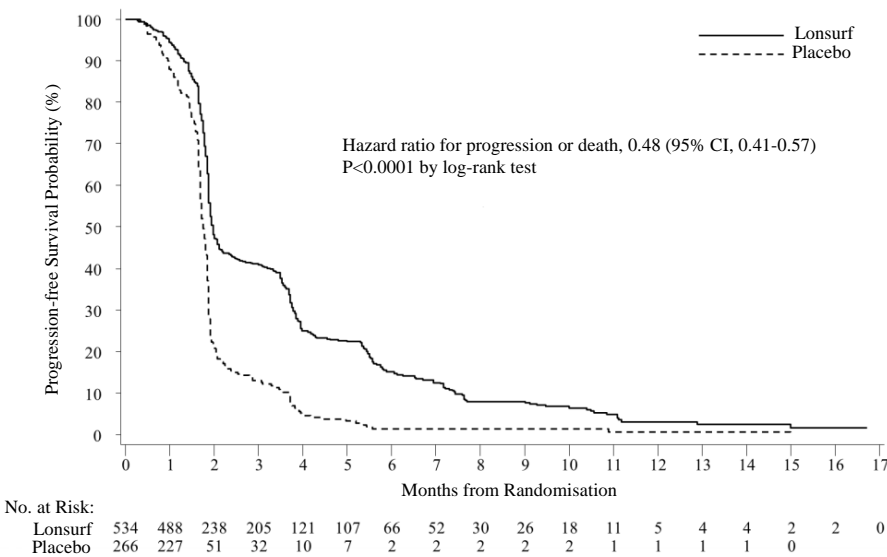
<sup>c</sup> Stratified log-rank test (strata: KRAS status, time since diagnosis of first metastasis, region)



**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 Lonsurf 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 Lonsurf 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 Lonsurf 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 Lonsurf 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 Lonsurf (44% vs 16%,  $p < 0.0001$ ).

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  $\geq 2$  for the Lonsurf 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 Lonsurf in combination with bevacizumab versus Lonsurf*

The clinical efficacy and safety of Lonsurf in combination with bevacizumab, versus Lonsurf 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 Lonsurf with bevacizumab (N = 246) or Lonsurf monotherapy (N = 246).

Patients received Lonsurf (starting dose of 35 mg/m<sup>2</sup>) 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%  $\geq 65$  years of age and 12%  $\geq 75$  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 Lonsurf-bevacizumab group and 2 months in the Lonsurf 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.

Lonsurf in combination with bevacizumab resulted in a statistically significant improvement in OS and PFS compared to Lonsurf 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**

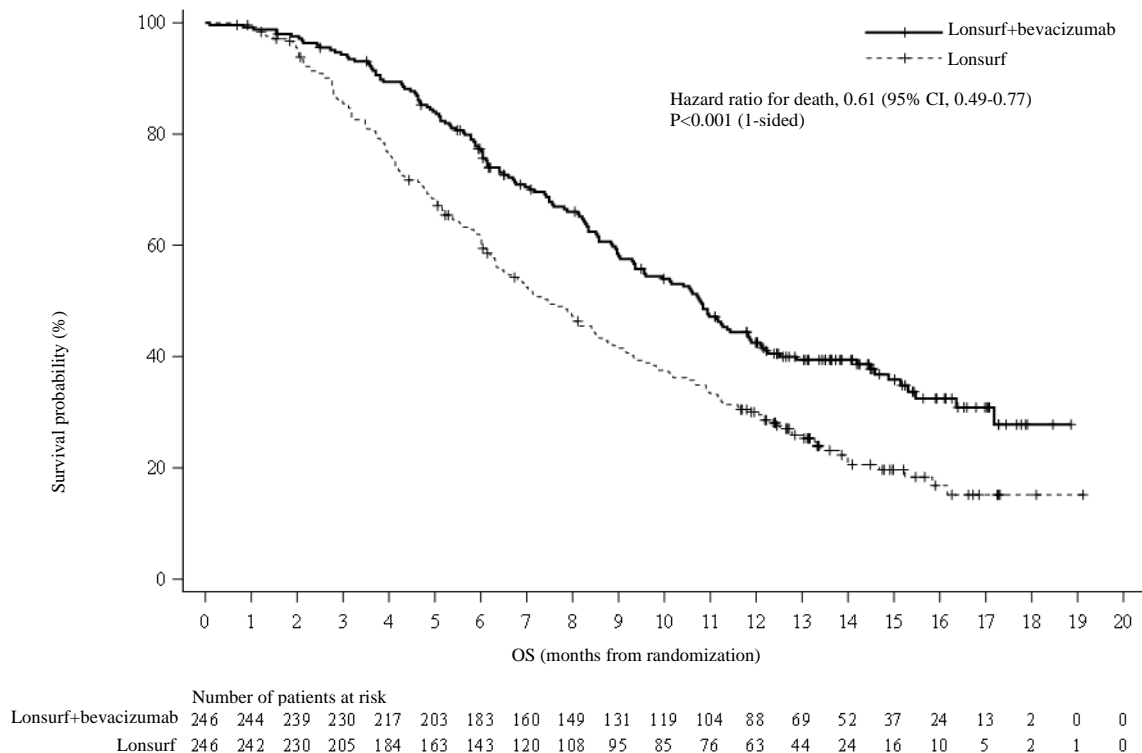
	<b>Lonsurf plus bevacizumab (N=246)</b>	<b>Lonsurf (N=246)</b>
<b>Overall survival</b>		
Number of deaths, N (%)	148 (60.2)	183 (74.4)
Median OS (months) <sup>a</sup> [95% CI] <sup>b</sup>	10.8 [9.4, 11.8]	7.5 [6.3, 8.6]
Hazard ratio [95% CI]	0.61 [0.49, 0.77]	
P-value <sup>c</sup>	< 0.001 (1-sided)	
<b>Progression-free survival (per investigator)</b>		
Number of progression or death, N (%)	206 (83.7)	236 (95.9)
Median PFS (months) <sup>a</sup> [95% CI] <sup>b</sup>	5.6 [4.5, 5.9]	2.4 [2.1, 3.2]
Hazard ratio [95% CI]	0.44 [0.36, 0.54]	
P-value <sup>c</sup>	< 0.001 (1-sided)	

<sup>a</sup> Kaplan-Meier estimates

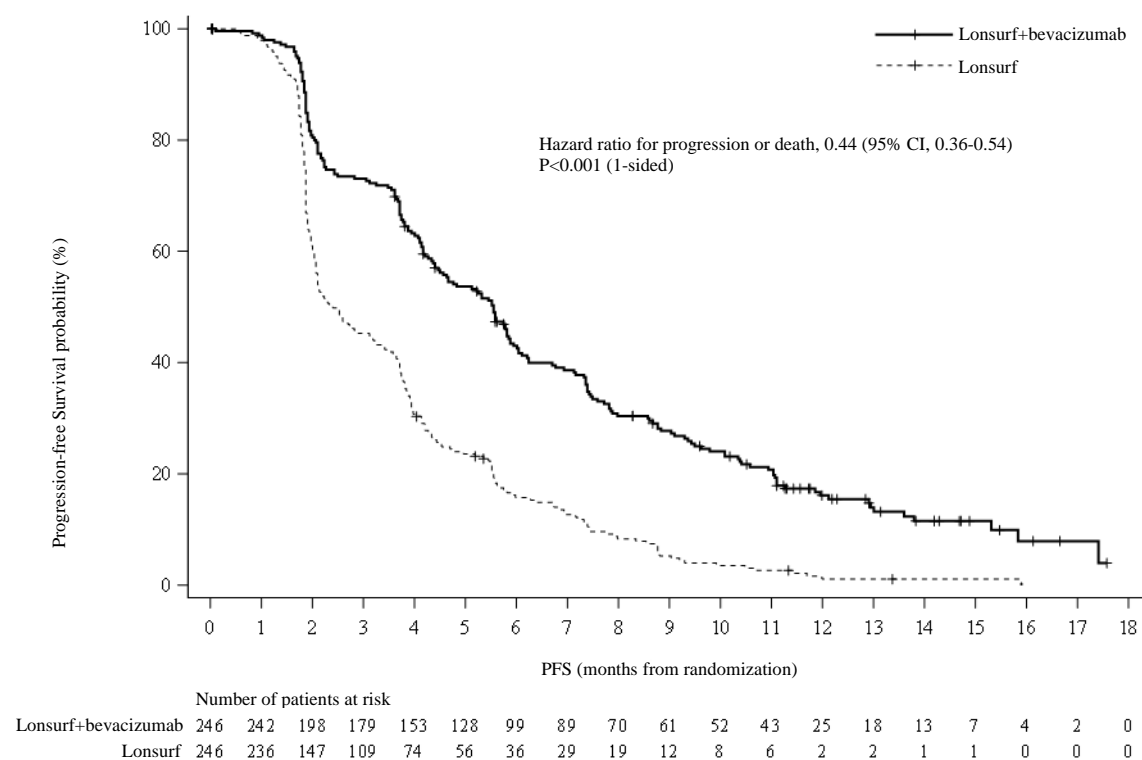
<sup>b</sup> Methodology of Brookmeyer and Crowley

<sup>c</sup> 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 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 by the investigator/local radiologist every 8 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<sup>2</sup>/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 Lonsurf 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 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 1-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 9, Figure 5 and Figure 6).

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

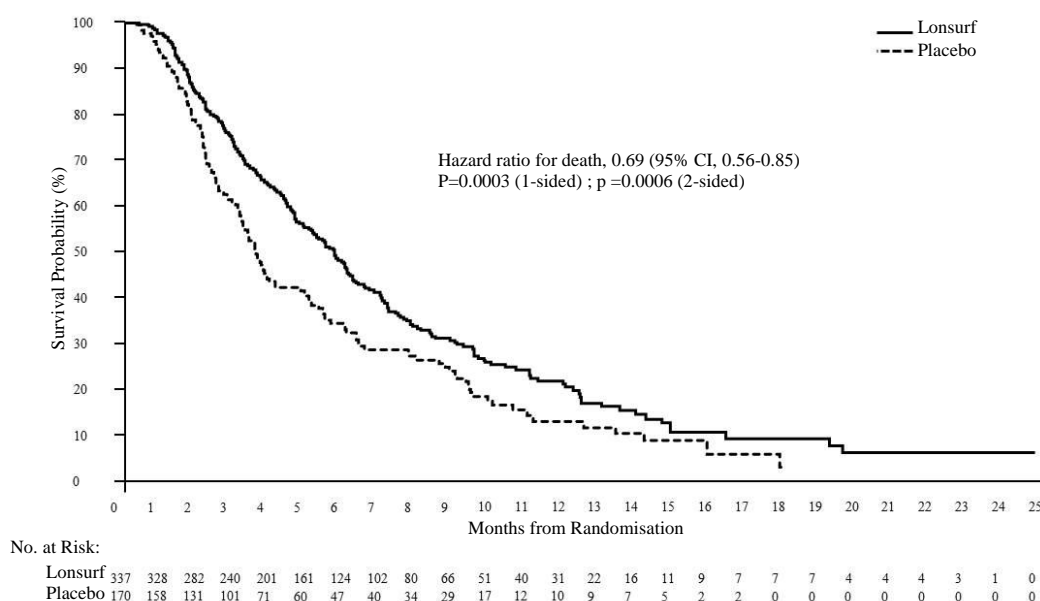
	<b>Lonsurf plus BSC (N=337)</b>	<b>Placebo plus BSC (N=170)</b>
<b>Overall survival</b>		
Number of deaths, N (%)	244 (72.4)	140 (82.4)
Median OS (months) <sup>a</sup> [95% CI] <sup>b</sup>	5.7 [4.8, 6.2]	3.6 [3.1, 4.1]
Hazard ratio [95% CI]	0.69 [0.56, 0.85]	
P-value <sup>c</sup>	0.0003 (1-sided), 0.0006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

<sup>a</sup> Kaplan-Meier estimates

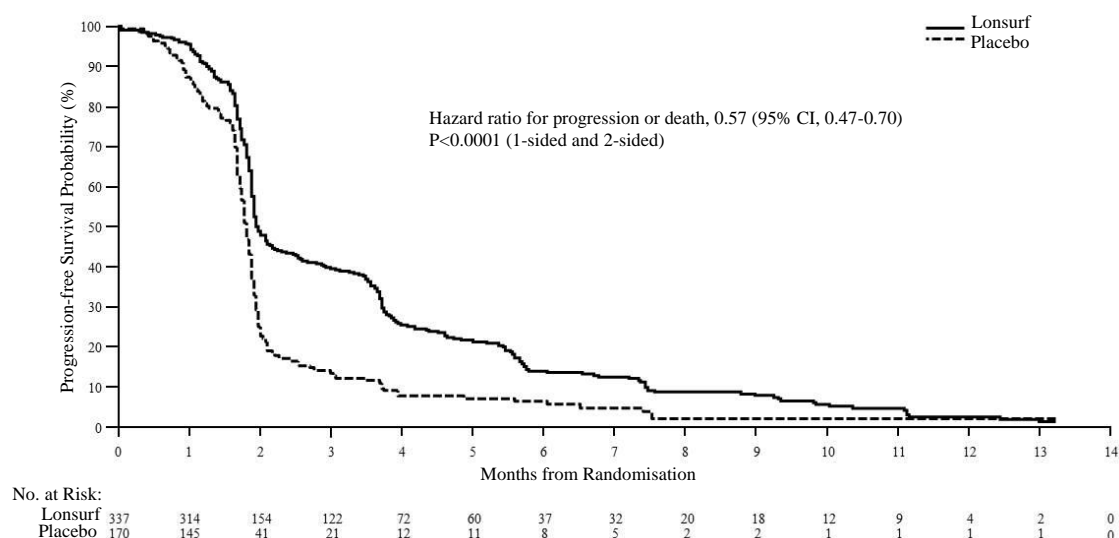
<sup>b</sup> Methodology of Brookmeyer and Crowley

<sup>c</sup> 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 Lonsurf (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 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.

### Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Lonsurf 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 Lonsurf 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 Lonsurf 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 Lonsurf 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 Lonsurf with [<sup>14</sup>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 [<sup>14</sup>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/m<sup>2</sup>) in patients with advanced solid tumours, the mean times to peak plasma concentrations (t<sub>max</sub>) 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<sup>2</sup>/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<sub>0-last</sub>) was approximately 3-fold higher and maximum concentration (C<sub>max</sub>) 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<sup>2</sup>/dose twice daily) in patients with advanced solid tumours, the mean times to peak plasma concentrations (t<sub>max</sub>) of trifluridine and tipiracil hydrochloride were around 2 hours and 3 hours, respectively.

#### *Contribution of tipiracil hydrochloride*

Single-dose administration of Lonsurf (35 mg/m<sup>2</sup>/dose) increased the mean AUC<sub>0-last</sub> of trifluridine by 37-fold and C<sub>max</sub> by 22-fold with reduced variability compared to trifluridine alone (35 mg/m<sup>2</sup>/dose).

#### *Effect of food*

When Lonsurf at a single dose of 35 mg/m<sup>2</sup> 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<sub>max</sub>, tipiracil hydrochloride C<sub>max</sub> 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).

#### 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<sup>2</sup>) 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 Lonsurf at the recommended dose and regimen, the mean elimination half-life (t<sub>1/2</sub>) 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<sub>1/2</sub> 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<sup>2</sup>) 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 [<sup>14</sup>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 [<sup>14</sup>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<sup>2</sup> twice daily), the AUC from time 0 to 10 hours (AUC<sub>0-10</sub>) 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<sup>2</sup>. 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 RECURSE 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). Patients with severe renal impairment received an adjusted starting dose of 20 mg/m<sup>2</sup> twice daily (reduced to 15 mg/m<sup>2</sup> 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<sub>max</sub> 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 renal 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 Cancer 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 Lonsurf is administered concomitantly with inhibitors of OCT2 and MATE1.

### Pharmacokinetic/pharmacodynamic relationship

The efficacy and safety of Lonsurf in metastatic colorectal cancer was compared between a high-exposure group (>median) and a low-exposure group ( $\leq$ 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  $\geq$ 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, Lonsurf 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). Lonsurf 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

##### *Lonsurf 15 mg/6.14 mg film-coated tablets*

Hypromellose  
Macrogol (8000)  
Titanium dioxide (E171)  
Magnesium stearate

##### *Lonsurf 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 and other handling**

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)**

EU/1/16/1096/001-006

## **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 25 April 2016

Date of latest renewal: 14 December 2020

## **10. DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

## **ANNEX II**

- A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

## **A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE**

Name and address of the manufacturers responsible for batch release

Les Laboratoires Servier Industrie  
905, route de Saran  
45520 Gidy  
France

Servier (Ireland) Industries Limited  
Gorey Road,  
Arklow,  
Co. Wicklow,  
Y14 E284,  
Ireland

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

## **B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

## **C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

## **D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

**ANNEX III**  
**LABELLING AND PACKAGE LEAFLET**

## **A. LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

**1. NAME OF THE MEDICINAL PRODUCT**

Lonsurf 15 mg/6.14 mg film-coated tablets  
trifluridine/tipiracil

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains 15 mg trifluridine and 6.14 mg of tipiracil (as hydrochloride).

**3. LIST OF EXCIPIENTS**

Contains lactose monohydrate, see leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

20 film-coated tablets  
40 film-coated tablets  
60 film-coated tablets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Oral use.  
Read the package leaflet before use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

Cytotoxic.

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**



**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Les Laboratoires Servier  
50 rue Carnot  
92284 Suresnes Cedex  
France

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/16/1096/001 20 film-coated tablets  
EU/1/16/1096/002 40 film-coated tablets  
EU/1/16/1096/003 60 film-coated tablets

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Lonsurf 15 mg/6.14 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC  
SN  
NN

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER**

**1. NAME OF THE MEDICINAL PRODUCT**

Lonsurf 15 mg/6.14 mg tablets  
trifluridine/tipiracil

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

Les Laboratoires Servier

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. OTHER**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

**1. NAME OF THE MEDICINAL PRODUCT**

Lonsurf 20 mg/8.19 mg film-coated tablets  
trifluridine/tipiracil

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

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

**3. LIST OF EXCIPIENTS**

Contains lactose monohydrate, see leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

20 film-coated tablets  
40 film-coated tablets  
60 film-coated tablets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Oral use.  
Read the package leaflet before use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

Cytotoxic.

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Les Laboratoires Servier  
50 rue Carnot  
92284 Suresnes Cedex  
France

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/16/1096/004 20 film-coated tablets  
EU/1/16/1096/005 40 film-coated tablets  
EU/1/16/1096/006 60 film-coated tablets

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Lonsurf 20 mg/8.19 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC  
SN  
NN

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER**

**1. NAME OF THE MEDICINAL PRODUCT**

Lonsurf 20 mg/8.19 mg tablets  
trifluridine/tipiracil

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

Les Laboratoires Servier

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. OTHER**

**B. PACKAGE LEAFLET**

## Package leaflet: Information for the patient

**Lonsurf 15 mg/6.14 mg film-coated tablets**

**Lonsurf 20 mg/8.19 mg film-coated tablets**  
trifluridine/tipiracil

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you experience any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See Section 4.

### **What is in this leaflet**

1. What Lonsurf is and what it is used for
2. What you need to know before you take Lonsurf
3. How to take Lonsurf
4. Possible side effects
5. How to store Lonsurf
6. Contents of the pack and other information

#### **1. What Lonsurf is and what it is used for**

Lonsurf is a type of cancer chemotherapy which belongs to the group of medicines called "cytostatic antimetabolite medicines".

Lonsurf contains two different active substances: trifluridine and tipiracil.

- Trifluridine stops the growth of cancer cells.
- Tipiracil stops the trifluridine from being broken down by the body, helping trifluridine to work longer.

Lonsurf is used to treat adults with colon or rectal cancer - sometimes called 'colorectal' cancer and stomach cancer (including cancer of the junction between the oesophagus and the stomach).

- It is used when the cancer has spread to other parts of the body (metastases).
- It is used when other treatments have not worked - or when other treatments are not suitable for you.

Lonsurf may be given in combination with bevacizumab. It is important that you also read the package leaflet of bevacizumab. If you have any questions about this medicine, ask your doctor.

#### **2. What you need to know before you take Lonsurf**

##### **Do not take Lonsurf**

- if you are allergic to trifluridine or tipiracil or any of the other ingredients of this medicine (listed in section 6).

Do not take Lonsurf if the above applies to you. If you are not sure, talk to your doctor before taking Lonsurf.

##### **Warnings and precautions**

Talk to your doctor or pharmacist before taking Lonsurf if:

- you have kidney problems
- you have liver problems

If you are not sure, talk to your doctor or pharmacist before taking Lonsurf.

Treatment may lead to the following side effects (see section 4):

- a reduced number of certain types of white blood cells (neutropenia) which are important for protecting the body against bacterial or fungal infections. As a consequence of neutropenia, fever (febrile neutropenia) and blood infection (septic shock) may occur
- a reduced number of red blood cells (anaemia)
- a reduced number of platelets in the blood (thrombocytopenia) which are important to stop bleeding and work by clumping and clotting blood vessel injuries
- gastrointestinal problems.

### **Tests and checks**

Your doctor will do blood tests before each cycle of Lonsurf. You start a new cycle every 4 weeks. The tests are needed because Lonsurf can sometimes affect your blood cells.

### **Children and adolescents**

This medicine is not indicated for use in children and adolescents below the age of 18 years. This is because it may not work or be safe.

### **Other medicines and Lonsurf**

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription and herbal medicines. This is because Lonsurf can affect the way some other medicines work. Also some other medicines can affect the way Lonsurf works.

In particular tell your doctor or pharmacist if you are taking medicines used for treatment of HIV, such as zidovudine. This is because zidovudine may not work as well if you are taking Lonsurf. Talk to your doctor about whether to switch to a different HIV medicine.

If the above applies to you (or you are not sure), talk to your doctor or pharmacist before taking Lonsurf.

### **Pregnancy and breast-feeding**

If you are pregnant or breast-feeding, or if you think you might be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. Lonsurf may harm your unborn baby.

If you become pregnant, you and your doctor will have to decide if the benefits of Lonsurf are greater than the risk of harm to the baby.

Do not breast-feed if you are taking Lonsurf as it is not known whether Lonsurf passes into the mother's milk.

### **Contraception**

You must not become pregnant while taking this medicine. This is because it may harm your unborn baby.

You and your partner should use effective methods of contraception while taking this medicine. You should also do this for 6 months after you stop taking the medicine. If you or your partner become pregnant during this time, you must talk to your doctor or pharmacist straight away.

### **Fertility**

Lonsurf may affect your ability to have a baby. Talk to your doctor for advice before using it.

### **Driving and using machines**

It is not known whether Lonsurf changes your ability to drive or use machines. Do not drive or use any tools or machines if you experience symptoms that affect your ability to concentrate and react.

### **Lonsurf contains lactose**

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

## **3. How to take Lonsurf**



Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

### **How much to take**

- Your doctor will decide the right dose for you - the dose depends on your weight and height and if you have kidney problems.
- Lonsurf comes in two strengths. Your doctor may prescribe both strengths for your prescribed dose.
- Your doctor will tell you how many tablets to take each time.
- You will take a dose 2 times a day.

### **When to take Lonsurf**

You will take Lonsurf for 10 days during the first 2 weeks, and then have 2 weeks off. This 4-week period is called a 'cycle.' The specific dosing schedule is as follows:

- **Week 1**
  - take the dose 2 times a day for 5 days
  - then have 2 days off - no medicine
- **Week 2**
  - take the dose 2 times a day for 5 days
  - then have 2 days off - no medicine
- **Week 3**
  - No medicine
- **Week 4**
  - No medicine

You will then start again with another cycle of 4 weeks following the above pattern.

### **How to take**

- Take this medicine by mouth.
- Swallow the tablets whole with a glass of water.
- Take within 1 hour after your morning and evening meals.
- Wash your hands after handling this medicine.

### **If you take more Lonsurf than you should**

If you take more Lonsurf than you should, talk to a doctor or go to a hospital straight away. Take your pack(s) of medicine with you.

### **If you forget to take Lonsurf**

- If you forget a dose, talk to your doctor or pharmacist.
- Do not take a double dose to make up for a forgotten dose.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

## **4. Possible side effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them. The following side effects may happen with this medicine when it is taken alone or in combination with bevacizumab:

### **Serious side effects**

**Tell your doctor immediately** if you notice any of the following serious side effects (many of the side effects are shown in laboratory tests - for example those affecting your blood cells):

- Neutropenia (*very common*), febrile neutropenia (*common*) and septic shock (*rare*). The signs include chills, fever, sweating or other signs of bacterial or fungal infection (see section 2).

- Anaemia (*very common*). The signs include feeling short of breath, tiredness or looking pale (see section 2).
- Vomiting (*very common*) and diarrhoea (*very common*), which may lead to a dehydration if severe or persistent.
- Severe gastrointestinal problems: abdominal pain (*common*), ascites (*rare*), colitis (*uncommon*), acute pancreatitis (*rare*), ileus (*uncommon*) and subileus (*rare*). The signs include intense stomach or abdominal pain that can be associated with vomiting, blocked or partly blocked bowel, fever or swelling of the abdomen.
- Thrombocytopenia (*very common*). The signs include unusual bruising or bleeding (see section 2).
- Pulmonary embolism (*uncommon*): blood clots in lungs. The signs include shortness of breath and pain in the chest or in the legs.
- Interstitial lung disease has been reported in patients receiving the medicine. The signs include difficulty in breathing, shortness of breath, with cough or fever.

Some of these serious side effects may lead to death.

### **Other side effects**

Tell your doctor if you notice any of the following side effects. Many of the side effects are shown in laboratory tests - for example those affecting your blood cells. Your doctor will be looking out for these side effects in your test results.

### **Very common: may affect more than 1 in 10 people:**

- decreased appetite
- feeling very tired (fatigue)
- feeling sick (nausea)
- reduced white blood cells called leucocytes - can increase your risk for infection
- swelling of mucous membranes in mouth

### **Common: may affect up to 1 in 10 people:**

- fever
- hair loss
- weight loss
- changes in taste
- constipation
- feeling generally out of sorts (malaise)
- low level of albumin in the blood
- increased bilirubin in your blood - can cause yellowing of skin or eyes
- reduced number of white blood cells called lymphocytes - can increase your risk for infection
- swelling in your hands or legs or feet
- mouth pain or problems
- swelling of mucous membranes - this could be inside the nose, throat, eyes, vagina, lungs or gut
- increased liver enzymes
- protein in your urine
- rash, itchy or dry skin
- feeling short of breath, airway or lungs, chest infections
- viral infection
- pain in your joints
- feeling dizzy, headache
- high blood pressure
- mouth ulcers
- muscle pain

### **Uncommon: may affect up to 1 in 100 people**

- low blood pressure
- blood test results indicating problems with clotting making you bleed more easily
- more noticeable heart-beat, chest pain

- abnormal increase or decrease in heart rate
- increased white blood cells
- increased number of white blood cells called monocytes
- increased lactate dehydrogenase level in your blood
- low levels of phosphates, sodium, potassium or calcium in your blood
- reduced white blood cells called monocytes - can increase your risk for infection
- high blood sugar (hyperglycaemia), increased urea, creatinine and potassium in your blood
- blood test result indicating inflammation (C-Reactive Protein increased)
- feeling of spinning (vertigo)
- runny or bloody nose, sinus problems
- sore throat, hoarse voice, problems with your voice
- redness, itching of the eye, eye infections, watery eyes
- dehydration
- bloating, passing gas, indigestion
- inflammation in lower part of digestive tract
- swelling or bleeding in your bowel
- inflammation or increased acid in your stomach or gullet, reflux
- painful tongue, retching
- tooth decay, tooth problems, gum infections
- skin flushing
- pain or discomfort in your arms or legs
- pain, including pain from the cancer
- bone pain, muscle weakness or spasms
- feeling of being cold
- shingles (pain and vesicular rash on skin over nerve tracts affected by nerve inflammation from herpes zoster virus)
- liver disorder
- inflammation or infection of bile ducts
- kidney failure
- cough, infection of the sinuses, throat infection
- infection in your bladder
- blood in urine
- problems passing water (urine retention), loss of bladder control (incontinence)
- changes in the menstrual cycle
- anxiety
- non-severe neurological troubles
- raised itchy rash, hives, acne
- sweating more than normal, nail problems
- problem with sleeping or falling asleep
- feeling of numbness or pins and needles in hands or feet
- redness, swelling, pain on the palms of your hands and soles of your feet (hand-foot syndrome)

**Rare: may affect up to 1 in 1 000 people**

- inflammation and infection in your gut
- athlete's foot - fungal infection of feet, yeast infections
- reduced white blood cells called granulocytes - can increase your risk for infection
- swelling or pain in your big toes
- swelling in your joints
- increased salt in your blood
- burning sensation, unpleasant, increased or loss of sense of touch
- fainting (syncope)
- vision troubles as blurred vision, double vision, decreased vision, cataracts
- dry eyes
- ear pain

- inflammation in upper part of digestive tract
- pain in upper or lower part of digestive tract
- accumulation of fluid in the lungs
- bad breath, gum problems, bleeding gums
- polyps inside your mouth
- inflammation or bleeding in your bowel
- increase in the diameter of the bile duct
- raised red skin, blisters, skin sloughing off
- sensitivity to light
- inflammation in your bladder
- changes in urine test
- blood clots, e.g. in the brain or legs
- changes in your heart trace (ECG - electrocardiogram)
- low level of total protein in the blood

### **Reporting of side effects**

If you experience any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

## **5. How to store Lonsurf**

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the outer carton or blister after “EXP.” The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

## **6. Contents of the pack and other information**

### **What Lonsurf contains**

Lonsurf 15 mg/6.14 mg film-coated tablet

- The active substances are trifluridine and tipiracil. Each film-coated tablet contains 15 mg trifluridine and 6.14 mg tipiracil
- The other ingredients are:
  - Tablet core: lactose monohydrate, starch pregelatinised (maize) and stearic acid (see section 2 “Lonsurf contains lactose”).
  - Film coat: hypromellose, macrogol (8000), titanium dioxide (E171), and magnesium stearate.
  - Printing ink: shellac, iron oxide red (E172), iron oxide yellow (E172), titanium dioxide (E171), indigo carmine aluminium lake (E132), carnauba wax and talc.

Lonsurf 20 mg/8.19 mg film-coated tablet

- The active substances are trifluridine and tipiracil. Each film-coated tablet contains 20 mg trifluridine and 8.19 mg tipiracil.
- The other ingredients are:
  - Tablet core: lactose monohydrate, starch pregelatinised (maize) and stearic acid (see section 2 “Lonsurf contains lactose”).
  - Film coating: hypromellose, macrogol (8000), titanium dioxide (E171), iron oxide red (E172), and magnesium stearate.

- Printing ink: shellac, iron oxide red (E172), iron oxide yellow (E172), titanium dioxide (E171), indigo carmine aluminium lake (E132), carnauba wax and talc.

**What Lonsurf looks like and contents of the pack**

- Lonsurf 15 mg/6.14 mg is a white, biconvex, round, film-coated tablet, printed with “15” on one side and “102” and “15 mg” on the other side in grey ink.
- Lonsurf 20 mg/8.19 mg is a pale red, biconvex, round, film-coated tablet, printed with “20” on one side and “102” and “20 mg” on the other side in grey ink.

Each pack contains 20 film-coated tablets (2 blisters of 10 tablets each) or 40 film-coated tablets (4 blisters of 10 tablets each), or 60 film-coated tablets (6 blisters of 10 tablets each). A desiccant is incorporated into each blister foil.

Not all pack sizes may be marketed.

**Marketing Authorisation Holder**

Les Laboratoires Servier  
50 rue Carnot  
92284 Suresnes Cedex  
France

**Manufacturer**

Les Laboratoires Servier Industrie  
905, route de Saran  
45520 Gidy  
France

Servier (Ireland) Industries Limited  
Gorey Road,  
Arklow,  
Co. Wicklow,  
Y14 E284,  
Ireland

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

**België/Belgique/Belgien**

S.A. Servier Benelux N.V.  
Tel: +32 (0)2 529 43 11

**България**

Сервие Медикал ЕООД  
Тел.: +359 2 921 57 00

**Česká republika**

Servier s.r.o.  
Tel: +420 222 118 111

**Danmark**

Servier Danmark A/S  
Tlf: +45 36 44 22 60

**Deutschland**

Servier Deutschland GmbH  
Tel: +49 (0)89 57095 01

**Eesti**

Servier Laboratories OÜ  
Tel: +372 664 5040

**Ελλάδα**

ΣΕΡΒΙΕ ΕΛΛΑΣ ΦΑΡΜΑΚΕΥΤΙΚΗ ΕΠΕ  
Τηλ: +30 210 939 1000

**España**

Laboratorios Servier S.L.  
Tel: +34 91 748 96 30

**France**

Les Laboratoires Servier  
Tel: +33 (0)1 55 72 60 00

**Hrvatska**

Servier Pharma, d. o. o.  
Tel.: +385 (0)1 3016 222

**Ireland****Lietuva**

UAB "SERVIER PHARMA"  
Tel: +370 (5) 2 63 86 28

**Luxembourg/Luxemburg**

S.A. Servier Benelux N.V.  
Tel: +32 (0)2 529 43 11

**Magyarország**

Servier Hungaria Kft.  
Tel: +36 1 238 7799

**Malta**

V.J. Salomone Pharma Ltd  
Tel: +356 21 22 01 74

**Nederland**

Servier Nederland Farma B.V.  
Tel: +31 (0)71 5246700

**Norge**

Servier Danmark A/S  
Tlf: +45 36 44 22 60

**Österreich**

Servier Austria GmbH  
Tel: +43 (1) 524 39 99

**Polska**

Servier Polska Sp. z o.o.  
Tel: +48 (0) 22 594 90 00

**Portugal**

Servier Portugal, Lda  
Tel.: +351 21 312 20 00

**România**

Servier Pharma SRL  
Tel: +4 021 528 52 80

**Slovenija**

Servier Laboratories (Ireland) Ltd.  
Tel: +353 (0)1 663 8110

**Ísland**

Servier Laboratories  
c/o Icepharma hf  
Sími: +354 540 8000

**Italia**

Servier Italia S.p.A.  
Tel: +39 06 669081

**Κύπρος**

C.A. Paraellinas Ltd.  
Τηλ: +357 22741741

**Latvija**

SIA Servier Latvia  
Tel: +371 67502039

Servier Pharma d. o. o.  
Tel.: +386 (0)1 563 48 11

**Slovenská republika**

Servier Slovensko spol. s r.o.  
Tel.:+421 (0) 2 5920 41 11

**Suomi/Finland**

Servier Finland Oy  
P. /Tel: +358 (0)9 279 80 80

**Sverige**

Servier Sverige AB  
Tel : +46 (0)8 522 508 00

**United Kingdom (Northern Ireland)**

Servier Laboratories (Ireland) Ltd.  
Tel: +44 (0)1753 666409

**This leaflet was last revised in**

**Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency web site:  
<http://www.ema.europa.eu>.