NAME OF THE MEDICINAL PRODUCT Lonsurf 15 mg/6.14 mg film-coated tablets. Lonsurf 20 mg/8.19 mg film-coated tablets. **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 of the summary of product characteristics. **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. **THERAPEUTIC INDICATIONS** Colorectal cancer Lonsurf is indicated as monotherapy for the treatment of adult patients with metastatic colorectal cancer (CRC) 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). **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 is 35 mg/m^2/dose administered orally twice daily on Days 1 to 5 and Days 8 to 12 of each 28-day cycle as long as benefit is observed or until unacceptable toxicity occurs (see section 4.4). The dosage is calculated according to body surface area (BSA) (see Table 1). The dosage 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 body surface area (BSA)

Starting dose	BSA (m²)	Dose in mg (2x daily)	Tablets per dose (2x daily)		Total daily dose (mg)
			15 mg/6,14mg	20 mg/8,19mg	
35 mg/m²	< 1,07	35	1	1	70
	1,07 - 1,22	40	0	2	80
	1,23 - 1,37	45	3	0	90
	1,38 - 1,52	50	2	1	100
	1,53 - 1,68	55	1	2	110
	1,69 - 1,83	60	0	3	120
	1,84 - 1,98	65	3	1	130
	1,99 - 2,14	70	2	2	140
	2,15 - 2,29	75	1	3	150
	≥ 2,30	80	0	4	160

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

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

Parameter	Interruption criteria	Resumption criteria[a]
Neutrophils	$<0,5 \times 10^9$/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 x 10^9/L) or thrombocytopenia (< 25 × 10^9/L) that results in more than 1 week's delay in start of next cycle • CTCAE* non-haematologic Grade 3 or Grade 4 adverse reaction; except for Grade 3 nausea and/or vomiting controlled by antiemetic therapy or diarrhoea responsive to antidiarrhoeal medicinal products	• Interrupt dosing until toxicity resolves to Grade 1 or baseline. • When resuming dosing, decrease the dose level by 5 mg/m^2/dose from the previous dose level (Table 4). • Dose reductions are permitted to a minimum dose of 20 mg/m^2/dose twice daily (or 15 mg/m^2/dose twice daily in severe renal impairment). • Do not increase dose after it has been reduced.

**Common terminology criteria for adverse events*

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

Reduced dose	BSA (m²)	Dose in mg (2x daily)	Tablets per dose (2x daily)		Total daily dose (mg)
			15 mg/ 6,14 mg	20 mg/ 8,19 mg	
Level 1 dose reduction: from 35 mg/m^2 to 30 mg/m^2					
30 mg/m²	<1,09	30	2	0	60
	1,09 - 1,24	35	1	1	70
	1,25 - 1,39	40	0	2	80
	1,40 - 1,54	45	3	0	90
	1,55 - 1,69	50	2	1	100
	1,70 - 1,94	55	1	2	110
	1,95 - 2,09	60	0	3	120
	2,10 - 2,28	65	3	1	130
	≥2,29	70	2	2	140
Level 2 dose reduction: from 30 mg/m² to 25 mg/m²					
25 mg/m²	<1,10	25[a]	2[a]	1[a]	50[a]
	1,10 - 1,29	30	2	0	60
	1,30 - 1,49	35	1	1	70
	1,50 - 1,69	40	0	2	80
	1,70 - 1,89	45	3	0	90
	1,90 - 2,09	50	2	1	100
	2,10 - 2,29	55	1	2	110
	≥2,30	60	0	3	120
Level 3 dose reduction: from 25 mg/m² to 20 mg/m²					
20 mg/m²	<1,14	20	0	1	40
	1.14 - 1.34	25[a]	2[a]	1[a]	50[a]
	1,35 - 1,59	30	2	0	60
	1,60 - 1,94	35	1	1	70
	1,95 - 2,09	40	0	2	80
	2,10 - 2,34	45	3	0	90
	≥2,35	50	2	1	100

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

Special populations: *Renal impairment • Mild renal impairment (CrCl 60 to 89 mL/min) or moderate renal impairment (CrCl 30 to 59 mL/min):* No adjustment of the starting dose is recommended in patients with mild or moderate renal impairment (see sections 4.4 and 5.2). • *Severe renal impairment (CrCl 15 to 29 mL/min):* For patients with severe renal impairment a starting dose of 20 mg/m^2 twice daily is recommended (see sections 4.4 and 5.2). One dose reduction to a minimum dose of 15 mg/m^2 twice daily is permitted based on individual safety and tolerability (see Table 5). Dose escalation is not permitted after it has been reduced. In the event of haematological and/or non-haematological toxicities patients should follow the dose interruption, resumption and reduction criteria stated in Table 2, Table 3 and Table 5.

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

Reduced dose	BSA (m²)	Dose in mg (2x daily)	Tablets per dose (2x daily)		Total daily dose (mg)
			15 mg/ 6,14 mg	20 mg/ 8,19 mg	
Starting dose					
30 mg/m²	< 1,14	20	0	1	40
	1,14 – 1,34	25[a]	2[a]	1[a]	50[a]
	1,35 – 1,59	30	2	0	60
	1,60 – 1,94	35	1	1	70
	1,95 – 2,09	40	0	2	80
	2,10 – 2,34	45	3	0	90
	≥ 2,35	50	2	1	100
Dose reduction: from 20 mg/m² to 15 mg/m²					
25 mg/m²	< 1,15	15	1	0	30
	1,15 – 1,49	20	0	1	40
	1,50 – 1,84	25[a]	2[a]	1[a]	50[a]
	1,85 – 2,09	30	2	0	60
	2,10 – 2,34	35	1	1	70
	≥ 2,35	40	0	2	80

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

End stage renal disease (CrCl below 15 mL/min or requiring dialysis): Administration is not recommended in patients with end stage renal disease as there are no data available for these patients (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. **CONTRAINDICATIONS** Hypersensitivity to the active substances or to any of the excipients listed in section 6.1 of the SPC. **SPECIAL WARNINGS AND PRECAUTIONS FOR USE** *Bone marrow suppression:* Complete blood cell counts must be obtained prior to initiation of therapy, prior to each cycle and as needed. Treatment must not be started if absolute neutrophil count < 1.5 x10^9/L, if platelet counts < 75x10^9/L, or if unresolved Grade 3 or 4 non-haematological clinically relevant toxicity. Patient should be monitored closely for infections, appropriate measures should be administered as clinically indicated. *Gastrointestinal toxicity:* anti-emetic, anti-diarrhoeal and other measures should be administered as clinically indicated, dose modifications should be applied as necessary. *Renal impairment:* not recommended if end-stage renal disease. Patients with renal impairment should be monitored closely; patients with moderate or severe renal impairment should be more frequently monitored for haematological toxicities. *Hepatic impairment:* not recommended if baseline moderate or severe hepatic impairment. *Proteinuria:* monitoring by dipstick urinalysis

recommended prior to starting and during therapy. Excipients: contain lactose. **INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION*** Precautions: medicinal products that interact with nucleoside transporters CNT1, ENT1 and ENT2, inhibitors of OCT2 or MATE1, human thymidine kinase substrates (e.g. zidovudine), hormonal contraceptives. **FERTILITY, PREGNANCY AND LACTATION*** Not recommended. **EFFECTS ON ABILITY TO DRIVE AND USE MACHINES*** Fatigue, dizziness or malaise may occur. **UNDESIRABLE EFFECTS** **Summary of safety profile**: The most serious observed adverse drug reactions in patients receiving Lonsurf are bone marrow suppression and gastrointestinal toxicity (see section 4.4). The most frequently observed adverse drug reactions (≥ 30%) in patients receiving Lonsurf are neutropenia (53% [34% ≥ Grade 3]), nausea (34% [1% ≥ Grade 3]), fatigue (32% [4% ≥ Grade 3]), anaemia (32% [12% ≥ Grade 3]). The most common adverse drug reactions (≥ 2%) in patients receiving Lonsurf that resulted in treatment discontinuation, dose reduction, dose delay, or dose interruption were neutropenia, anaemia, leukopenia, fatigue, thrombocytopenia, nausea and diarrhoea. List of adverse drug 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 the 335 treated patients with metastatic gastric cancer in the placebo-controlled Phase III (TAGS) clinical trial, are shown below. 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 drug reactions are grouped according to their frequencies. Frequency groups are defined by the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); and uncommon (≥1/1,000 to < 1/100). Within each frequency group, adverse drug reactions are presented in order of decreasing seriousness. **Infections and infestations:** *Common:* Lower respiratory tract infection. *Uncommon:* Septic shock[b], enteritis infectious, lung infection, biliary tract infection, influenza, urinary tract infection, gingivitis, herpes zoster, tinea pedis, candida infection, bacterial infection, infection, neutropenic sepsis, upper respiratory tract infection, conjunctivitis. **Neoplasms benign, malignant and unspecified (incl. cysts and polyps):** *Uncommon:* Cancer pain. **Blood and lymphatic system disorders:** *Very Common:* neutropenia, leukopenia, anaemia, thrombocytopenia. *Common:* Febrile neutropenia, lymphopenia. *Uncommon:* Pancytopenia, granulocytopenia, monocytopenia, erythropenia, leucocytosis, monocytosis. **Metabolism and nutrition disorders:** *Very common:* Decreased appetite. *Common:* Hypoalbuminaemia. *Uncommon:* Dehydration, hyperglycaemia, hyperkalaemia, hypokalaemia, hypophosphataemia, hypernatraemia, hyponatraemia, hypocalcaemia, gout. **Psychiatric disorders:** *Uncommon:* Anxiety, insomnia. **Nervous system disorders:** *Common:* Dysgeusia, neuropathy peripheral. *Uncommon:* Neurotoxicity, dysaesthesia, hyperaesthesia, hypoaesthesia, syncope, paraesthesia, burning sensation, lethargy, dizziness, headache. **Eye disorders:** *Uncommon:* Visual acuity reduced, vision blurred, diplopia, cataract, dry eye. **Ear and labyrinth disorders:** *Uncommon:* Vertigo, ear discomfort. **Cardiac disorders:** *Uncommon:* Angina pectoris, arrhythmia, palpitations. **Vascular disorders:** *Uncommon:* Embolism, hypertension, hypotension, flushing. **Respiratory, thoracic and mediastinal disorders:** *Common:* Dyspnoea. *Uncommon:* Pulmonary embolism[b], pleural effusion, rhinorrhoea, dysphonia, oropharyngeal pain, epistaxis, cough. **Gastrointestinal disorders:** *Very common:* Diarrhoea, nausea, vomiting. *Common:* Abdominal pain Constipation, stomatitis, oral disorder. *Uncommon:* 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:** *Common:* Hyperbilirubinaemia. *Uncommon:* Hepatotoxicity, biliary dilatation. **Skin and subcutaneous tissue disorders:** *Common:* Palmar-plantar erythrodysaesthesia syndrome[c], rash, alopecia, pruritus, dry skin. *Uncommon:* Skin exfoliation, urticaria, photosensitivity reaction, erythema, acne, hyperhidrosis, blister, nail Disorder. **Musculoskeletal and connective tissue disorders:** *Uncommon:* Joint swelling, arthralgia, bone pain, myalgia, musculoskeletal pain, muscular weakness, muscle spasms, pain in extremity. **Renal and urinary disorders:** *Common:* Proteinuria. *Uncommon:* Renal failure, cystitis noninfective, micturition disorder, haematuria, leukocyturia. **Reproductive system and breast disorders:** *Uncommon:* Menstrual disorder. **General disorders and administration site conditions:** *Very common:* Fatigue. *Common:* Pyrexia, oedema, mucosal inflammation, malaise. *Uncommon:* General physical health deterioration, pain, feeling of body temperature change, xerosis, discomfort. **Investigations:** *Common:* Hepatic enzyme increased, blood alkaline phosphatase increased, weight decreased. *Uncommon:* 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. Elderly: Patients 65 years of age or older who received Lonsurf had a higher incidence of the following events compared to patients younger than 65 years: - metastatic coloreactal cancer (RECOURSE): Grade 3 or 4 neutropenia (48% vs 30%), Grade 3 anaemia (26% vs 12%), Grade 3 or 4 leukopenia (26% vs 18%) and Grade 3 or 4 thrombocytopenia (9% vs 2%). - metastatic gastric cancer (TAGS): Grade 3 or 4 neutrophil count decrease (17.0% vs 6.6%), decreased appetite (37.3% vs 31.9%), asthenia (22.2% vs 17.0%) and stomatitis (7.2% vs 2.2%). Infections: In the Phase III clinical trials, treatment-related infections occurred more frequently in Lonsurf-treated patients (5.8%) compared to those receiving placebo (1.8%). Proteinuria:

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). 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 vs. those that did not. 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 **Belgium,** Federal Agency for Medicines and Health Products, Department Vigilance - Mailbox 97, B-1000 Brussels Madou, Website: www.fagg.be - Email: adversedrugreactions@fagg-afmps.be. **Luxemburg,** Direction de la Santé - Division de la Pharmacie et des Médicaments - Allée Marconi - Villa Louvigny, L-2120 Luxembourg, Fax: +352 2479 5615 E-mail: pharmacovigilance@ms.etat.lu Link pour le formulaire: http://www.sante.public.lu/fr/politique-sante/ministere-sante/direction-sante/div-pharmacie-medicaments/index.html **OVERDOSE* PHARMACODYNAMIC PROPERTIES*** Trifluridine is an antineoplastic thymidine-based nucleoside analogue and tipiracil hydrochloride is a thymidine phosphorylase (TPase) inhibitor. 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, preventing 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. **PACKAGING** Each pack contains 20 film-coated tablets. **MARKETING AUTHORISATION HOLDER** Les Laboratoires Servier - 50 rue Carnot - 92284 Suresnes Cedex France. **MARKETING AUTHORISATION NUMBER(S)** EU/1/16/1096/001-006. **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE** Medicinal product subject to restricted medical prescription. **DATE OF REVISION OF THE TEXT** 12/2020. Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu. *for full information, see SPC.

BE LS NA 12 20 – date of approval of the abbreviated SPC: 15/12/2020.

Lonsurf® trifluridine/tipiracil	Price ex-factory excl. VAT
15 mg / 6,14 mg x 20 tablets	€ 575,00
20 mg / 8,19 mg x 20 tablets	€ 766,67