

# Product Information

## NAME OF THE MEDICINE

ORCANTAS 15/6.14

Trifluridine 15 mg/ tipiracil hydrochloride 7.065 mg (equivalent to tipiracil 6.14 mg)

ORCANTAS 20/8.19

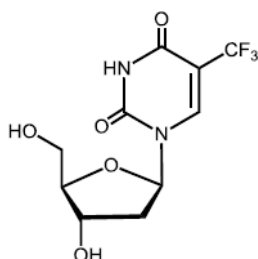
Trifluridine 20 mg/ tipiracil hydrochloride 9.420 mg (equivalent to tipiracil 8.19 mg)

The active components of ORCANTAS are trifluridine and tipiracil hydrochloride.

### *Trifluridine*

Trifluridine has the chemical name 2'-deoxy-5-(trifluoromethyl)uridine

*Chemical structure:*



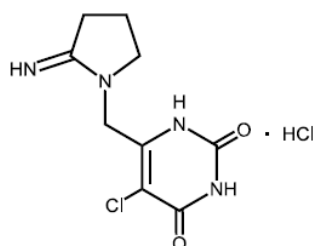
*Molecular formula:* C<sub>10</sub>H<sub>11</sub>F<sub>3</sub>N<sub>2</sub>O<sub>5</sub> (Relative Molecular Mass: 296.20)

*CAS Registry Number:* 70-00-8

### *Tipiracil hydrochloride*

Tipiracil hydrochloride has the chemical name 5-chloro-6-[(2-iminopyrrolidin-1-yl)methyl]pyrimidine-2,4-(1H,3H)-dione monohydrochloride.

*Chemical structure:*



*Molecular formula:* C<sub>9</sub>H<sub>11</sub>ClN<sub>4</sub>O<sub>2</sub>·HCl (Relative Molecular Mass: 279.12)

*CAS Registry Number:* 183204-72-0

## DESCRIPTION

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

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

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*Excipients:*

Tablet core- Lactose monohydrate, pre-gelatinised starch, stearic acid.

Film-coating- titanium dioxide, hypromellose, macrogol (8000), magnesium stearate, iron oxide red (E172) (specific to ORCANTAS 20/8.19)

Ink imprinting- indigo carmine aluminium lake (E132), iron oxide yellow (E172), iron oxide red (E172), shellac, carnauba wax, talc, titanium dioxide (E171).

**PHARMACOLOGY**

Pharmacodynamics

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

ORCANTAS is comprised of an antineoplastic thymidine-based nucleoside analogue, trifluridine, and the thymidine phosphorylase (TPase) inhibitor, tipiracil hydrochloride, at a molar ratio 1:0.5 (weight ratio, 1:0.471).

Following uptake into cancer cells, trifluridine, is phosphorylated by thymidine kinase, further metabolised in cells to a deoxyribonucleic acid (DNA) substrate, and incorporated directly into DNA, thereby interfering with DNA function to prevent cell proliferation. However, trifluridine is rapidly degraded by thymidine phosphorylase (TPase) and readily metabolised by a first-pass effect following oral administration, hence the inclusion of the thymidine phosphorylase inhibitor, tipiracil hydrochloride.

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

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

*Pre-clinical data*

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

Pharmacokinetics

*Absorption*

After oral administration of ORCANTAS 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 ORCANTAS 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 ORCANTAS (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.

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In the pharmacokinetic (PK) analyses of the multiple dose administration of ORCANTAS (35 mg/m<sup>2</sup>/dose, twice daily for 5 days a week with 2 days rest for 2 weeks followed by a 14-day rest, repeated every 4 weeks), trifluridine area under the concentration-time curve from time 0 to the last measurable concentration (AUC<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 ORCANTAS 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 ORCANTAS. Following multiple doses of ORCANTAS (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 ORCANTAS (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 ORCANTAS 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 ORCANTAS was administered within 1 hour after completion of the morning and evening meals (see *DOSAGE AND ADMINISTRATION* section).

### *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 ORCANTAS (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. 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 ORCANTAS 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 ORCANTAS (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 ORCANTAS 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 ORCANTAS

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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> BID), the 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 pharmacokinetic analysis, there is no clinically relevant effect of age, gender or race on the pharmacokinetics of trifluridine or tipiracil hydrochloride.

#### *Renal impairment*

Of the 533 patients in the RECURSE study who received ORCANTAS, 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 ORCANTAS 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 ORCANTAS 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. The PK of trifluridine and tipiracil hydrochloride have not been studied in patients with severe renal impairment or end-stage renal disease (see *PRECAUTIONS* section).

#### *Hepatic impairment*

Based on the population pharmacokinetic analysis, liver function parameters including alkaline phosphatase (ALP, 36-2,322 U/L), aspartate aminotransferase (AST, 11-197 U/L), alanine aminotransferase (ALT, 5-182 U/L), and total bilirubin (0.17-3.20 mg/dL) were not significant covariates for pharmacokinetics parameters of either trifluridine or tipiracil hydrochloride. Serum albumin was found to significantly affect trifluridine clearance, with a negative correlation. For low albumin values ranging from 2.2 to 3.5 g/dL, the corresponding clearance values range from 4.2 to 3.1 L/h. In a dedicated study, the PK of trifluridine and tipiracil hydrochloride were evaluated in cancer patients with mild or moderate hepatic impairment (National Cancer Institute [NCI] Criteria Group B and C, respectively) and in patients with normal hepatic function, no clinically important differences in the mean exposure were observed. Based upon limited data with a considerable variability, no statistically significant differences were observed in the pharmacokinetics in patients with normal hepatic function versus patients with mild or moderate hepatic impairment. Five out of six patients with moderate hepatic impairment and 2 out of 8 patients in the control group experienced Grade 3 or 4 increased bilirubin levels. No correlation was seen for trifluridine nor tipiracil hydrochloride between PK parameters and AST or/and total blood bilirubin. Half-life time (t<sub>1/2</sub>) and the accumulation ratio of trifluridine and tipiracil hydrochloride were similar between the moderate, mild and normal hepatic function patients. Enrolment into the dedicated hepatic impairment study was discontinued due to the high incidence of Grade 3 or 4 increased bilirubin levels in patients with moderate hepatic impairment. There is no need for a starting dose adjustment in patients with mild hepatic impairment (see *DOSAGE AND ADMINISTRATION* section). The use of ORCANTAS is not recommended in patients with baseline moderate or severe

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hepatic impairment due to the observed high incidence of Grade 3 or 4 hyperbilirubinaemia in patients with baseline moderate hepatic impairment (see *PRECAUTIONS* section).

*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 and FTY had no inductive effect on human CYP1A2, CYP2B6 or CYP3A4/5. Thus trifluridine is not expected to cause or be subject to a significant medicinal product interaction mediated by CYP. Inductive effect of tipiracil on human CYP isoforms cannot be excluded.

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

*Pharmacokinetic/pharmacodynamic relationship*

The efficacy and safety of ORCANTAS 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%).

**CLINICAL TRIALS**

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

In total, 800 patients were randomized 2:1 to receive ORCANTAS (N=534) plus best supportive care (BSC) or matching placebo (N=266) plus BSC. ORCANTAS dosing was based on body surface area (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 five days a week with a two-day rest for two weeks, followed by a 14-day rest, repeated every four weeks. Patients continued therapy until disease progression or unacceptable toxicity (see *DOSAGE AND ADMINISTRATION* section).

Of the 800 randomized patients, the median age was 63 years, 61% were male, 58% and 35% were Caucasian and Asian respectively, and 1% were African American. All patients had baseline Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of zero or one. The primary site of disease was the colon (62%) or the rectum (38%). KRAS status was wild (49%) or



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mutant (51%) at study entry. The median number of prior lines of therapy for metastatic disease was three. All patients received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy. All but one patient received bevacizumab, and all but two patients with KRAS wild type tumors received panitumumab or cetuximab. The two treatment groups were comparable with respect to demographic and baseline disease characteristics.

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

**Table 1: Efficacy Results (Intent-To-Treat Population) from the Phase III (RECOURSE) clinical trial**

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

<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)

<sup>d</sup> Using log-log transformation methodology of Kalbfleisch and Prentice

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

**Table 2: Efficacy Results (Tumour-Response (TR) population) from the Phase III (RECOURSE) clinical trial**

	<b>ORCANTAS plus BSC (N=502)</b>	<b>Placebo plus BSC (N=258)</b>
<b>Overall Response Rate and Disease Control Rate (TR population )</b>		

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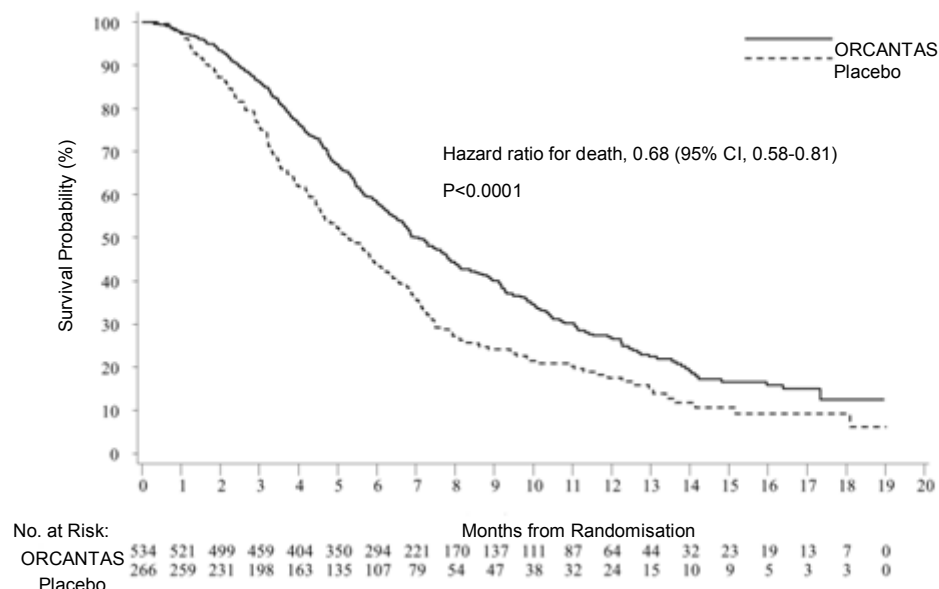
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	<b>ORCANTAS plus BSC (N=502)</b>	<b>Placebo plus BSC (N=258)</b>
ORR (Complete or partial),	8 (1.6) [0.7, 3.1]	1/258 (0.4) [0.0, 2.1]
P-value <sup>f</sup>	0.2862	
DCR (complete, partial or stable disease), n (%) [95% CI]	221 (44.0) [39.6, 48.5]	42/258 (16.3) [12.0, 21.4]
P-value <sup>f</sup>	<0.0001	

<sup>e</sup> Exact 2-sided confidence interval based on Clopper-Pearson methodology

<sup>f</sup> Fisher's Exact test (2-sided)

**Figure 1- Kaplan-Meier Curves of Overall Survival (Intent-To-Treat Population)**



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.

Sixty one percent (61%, n=485) of all randomized patients received a fluoropyrimidine as part of their last treatment regimen prior to randomization, of which 455 (94%) were refractory to the fluoropyrimidine at that time. Among these patients, OS benefit with ORCANTAS remained favourable (HR=0.75, 95% CI 0.59 to 0.94).

Treatment with ORCANTAS plus BSC resulted in a statistically significant prolongation of PS < 2 in comparison to placebo plus BSC. The median time to PS ≥ 2 for the ORCANTAS group and placebo group was 5.7 months and 4.0 months, respectively, with a hazard ratio (HR) of 0.66 (95% CI: 0.56, 0.78), p < 0.0001.

Elderly

There is limited data in patients aged between 75 and 84 years (N=60). There were no patients aged ≥ 85 years in the RECURSE study and the Japanese phase 2 study. The effect of ORCANTAS on overall survival was similar in patients aged <65 years and ≥65 years.

**INDICATIONS**

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

**CONTRAINDICATIONS**

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

**PRECAUTIONS**

The safety of ORCANTAS has not been studied in patients with mCRC with an Eastern Cooperative Oncology Group (ECOG) performance status  $\geq 2$ .

**Bone Marrow Suppression**

ORCANTAS caused an increase in the incidence of myelosuppression including anaemia, neutropenia, leucopenia, 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 (ANC) 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 ORCANTAS (see *ADVERSE EFFECTS* section). Given that the majority were reported in the context of bone marrow suppression, the patient's condition should be monitored closely and appropriate measures such as antimicrobial medicines and Granulocyte-Colony Stimulating Factor (G-CSF), should be administered as clinically indicated. In the REOURSE study, 9.4% of patients in the ORCANTAS group received G-CSF mainly for therapeutic use.

**Gastrointestinal Toxicity**

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

Patients with nausea, vomiting, diarrhoea and other gastrointestinal toxicities should be carefully monitored. Appropriate measures such as antiemetic, antidiarrhoeal, and/or fluid/electrolyte replacement therapy should be administered as clinically indicated. Dose modifications (delay and/or reduction) should be applied as necessary (see *DOSAGE AND ADMINISTRATION* section).

**Renal impairment**

ORCANTAS is not recommended for use in patients with severe renal impairment or end-stage renal disease (creatinine clearance [CrCl]  $< 30$  mL/min or requiring dialysis, respectively), as it has not been studied in these patients (see *PHARMACOLOGY-Pharmacokinetics* section).

Patients with moderate renal impairment (CrCl = 30 to 59 mL/min) had a higher incidence (defined as a difference of at least 5%) of  $\geq$  Grade 3 adverse events (AEs), serious AEs, and dose delays and reductions compared to the patients with normal (CrCl  $\geq 90$  mL/min) or mild renal impairment (CrCl = 60 to 89 mL/min). In addition, a higher exposure of trifluridine and tipiracil was observed in patients with moderate renal impairment, compared with patients with normal renal function or patients with mild renal impairment (see *PHARMACOLOGY-Pharmacokinetics* section).

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

**Hepatic impairment**



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ORCANTAS is not recommended for use in patients with baseline moderate or severe hepatic impairment (National Cancer Institute [NCI] Criteria Group C and D) defined by total bilirubin > 1.5 x ULN), as a higher incidence of Grade 3 or 4 hyperbilirubinaemia is observed in patients with baseline moderate hepatic impairment, although this is based on very limited data (see *PHARMACOLOGY-Pharmacokinetics* section).

Proteinuria

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

Lactose intolerance

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

Effects on Fertility

There are no data available on the effect of ORCANTAS on human fertility.

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

Use in Pregnancy (Category D)

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

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

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

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

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

Use in Lactation

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

### Paediatric Use

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

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

### Use in the Elderly

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

### Genotoxicity and Carcinogenicity

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

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

### Effect on ability to drive or operate machinery

ORCANTAS might interfere with the ability to drive and operate machinery. Fatigue, dizziness or malaise may occur during treatment (see *ADVERSE EFFECTS* section).

## **INTERACTIONS WITH OTHER MEDICINES**

*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 and FTY had no inductive effect on human CYP isoforms (see *PHARMACOLOGY-Pharmacokinetics* section). Inductive effect of tipiracil on human CYP isoforms cannot be excluded.

### Medicines that are inhibitors of OCT2 or MATE1.

*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 ORCANTAS is administered concomitantly with inhibitors of OCT2 or MATE1.

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

Caution is required when using medicines that are human thymidine kinase substrates, e.g. zidovudine. Such medicines, if used concomitantly with ORCANTAS, may compete with the effector, trifluridine, for activation via thymidine kinases. Therefore, when using antiviral medicines that are human thymidine kinase substrates, monitor for possible decreased efficacy of the antiviral

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medicine, and consider switching to an alternative antiviral medicine that is not a human thymidine kinase substrate, such as lamivudine, zalcitabine, didanosine, and abacavir.

*Hormonal contraceptives*

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

**ADVERSE EFFECTS**

Summary of the safety profile

The most serious observed adverse drug reactions in patients receiving ORCANTAS are bone marrow suppression and gastrointestinal toxicity (see *PRECAUTIONS* section).

The most frequently observed adverse drug reactions ( $\geq 30\%$ ) in patients receiving ORCANTAS are neutropenia (54% [35%  $\geq$  Grade 3]), nausea (39% [1%  $\geq$  Grade 3]), fatigue (35% [4%  $\geq$  Grade 3]), anaemia (32% [13%  $\geq$  Grade 3]) and leucopenia (31% [12%  $\geq$  Grade 3]).

The most common adverse drug reactions in patients receiving ORCANTAS that resulted in treatment discontinuation, dose reduction, dose delay, or dose interruption were neutropenia, general deterioration of health, anaemia, febrile neutropenia, fatigue, diarrhoea and dyspnoea.

Tabulated list of adverse reactions

The adverse drug reactions observed from the 533 patients with metastatic colorectal cancer, treated with a starting dose of 35 mg/m<sup>2</sup> of ORCANTAS in the placebo-controlled Phase III (RECOURSE) clinical trial, are shown in Tables 3 and 4. They are classified according to System Organ Class (SOC) and the appropriate MedDRA term is used to describe the drug reaction and its synonyms and related conditions.

ADRs reported very commonly (i.e.  $\geq 10\%$  of patients) in patients treated with TAS-102 plus BSC compared with placebo plus BSC from the RECOURSE study are listed in Table 3 and presented by grade (all grades and  $\geq$  Grade 3).

**Table 3: Very common Adverse Drug Reactions (ADRs) Reported in Patients with Metastatic Colorectal Cancer treated with ORCANTAS in the Phase III (RECOURSE) clinical trial**

MedDRA SOC <sup>a</sup> Preferred Term	ORCANTAS (N=533) %		Placebo (N=265) %	
	All Grades	$\geq$ Grade 3	All Grades	$\geq$ Grade 3
<b>Blood And Lymphatic System Disorders</b>				
Anaemia	32.1	12.6	4.5	1.9
Leucopenia	31.0	11.8	0.4	0
Neutropenia	53.8	34.5	0.4	0
Thrombocytopenia	19.9	4.1	1.9	0.4
<b>Gastrointestinal Disorders</b>				
Diarrhoea	23.6	2.3	9.1	0
Nausea	39.4	0.9	10.9	0
Vomiting	20.1	0.6	4.5	0

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MedDRA SOC <sup>a</sup> Preferred Term	ORCANTAS (N=533) %		Placebo (N=265) %	
	All Grades	≥ Grade 3	All Grades	≥ Grade 3
<b>General Disorders And Administration Site Conditions</b> Fatigue	35.3	3.8	14.7	2.6
<b>Metabolism And Nutrition Disorders</b> Decreased Appetite	26.5	1.7	11.3	0

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

ADRs reported with a frequency < 10% in patients treated with TAS-102 plus BSC from the RECURSE study are listed in Table 4 below by MedDRA system organ class and by frequency: common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from available data). Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness.

**Table 4: Adverse Drug Reactions (ADRs) Reported in < 10% Of Patients with Metastatic Colorectal Cancer treated with ORCANTAS in the Phase III (RECURSE) clinical trial**

System Organ Class (MedDRA) <sup>a</sup>	Common	Uncommon
<b>Infections and infestations</b>	<ul style="list-style-type: none"> <li>– Lower respiratory tract infection</li> <li>– Upper respiratory tract infection</li> </ul>	<ul style="list-style-type: none"> <li>– Septic shock<sup>b</sup></li> <li>– Enteritis infectious</li> <li>– Lung infection</li> <li>– Biliary tract infection</li> <li>– Influenza</li> <li>– Urinary tract infection</li> <li>– Gingival infection</li> <li>– Herpes zoster</li> <li>– Tinea pedis</li> <li>– Candidiasis</li> <li>– Bacterial infection</li> <li>– Infection</li> </ul>
<b>Neoplasms benign, malignant and unspecified (incl. cysts and polyps)</b>		<ul style="list-style-type: none"> <li>– Cancer pain</li> </ul>
<b>Blood and lymphatic system disorders</b>	<ul style="list-style-type: none"> <li>– Febrile neutropenia</li> <li>– Lymphopenia</li> <li>– Monocytosis</li> </ul>	<ul style="list-style-type: none"> <li>– Pancytopenia</li> <li>– Granulocytopenia</li> <li>– Monocytopenia</li> <li>– Erythropenia</li> <li>– Leukocytosis</li> </ul>

<b>System Organ Class (MedDRA)<sup>a</sup></b>	<b>Common</b>	<b>Uncommon</b>
<b>Metabolism and nutrition disorders</b>	<ul style="list-style-type: none"> <li>– Hypoalbuminaemia</li> </ul>	<ul style="list-style-type: none"> <li>– Dehydration</li> <li>– Hyperglycaemia</li> <li>– Hyperkalaemia</li> <li>– Hypokalaemia</li> <li>– Hypophosphataemia</li> <li>– Hyponatraemia</li> <li>– Hyponatraemia</li> <li>– Hypocalcaemia</li> <li>– Gout</li> </ul>
<b>Psychiatric disorders</b>	<ul style="list-style-type: none"> <li>– Insomnia</li> </ul>	<ul style="list-style-type: none"> <li>– Anxiety</li> </ul>
<b>Nervous system disorders</b>	<ul style="list-style-type: none"> <li>– Dysgeusia</li> <li>– Neuropathy peripheral</li> <li>– Dizziness</li> <li>– Headache</li> </ul>	<ul style="list-style-type: none"> <li>– Neurotoxicity</li> <li>– Dysaesthesia</li> <li>– Hyperaesthesia</li> <li>– Hypoaesthesia</li> <li>– Syncope</li> <li>– Paraesthesia</li> <li>– Burning sensation</li> <li>– Lethargy</li> </ul>
<b>Eye disorders</b>		<ul style="list-style-type: none"> <li>– Visual acuity reduced</li> <li>– Vision blurred</li> <li>– Diplopia</li> <li>– Cataract</li> <li>– Conjunctivitis</li> <li>– Dry eye</li> </ul>
<b>Ear and labyrinth disorders</b>		<ul style="list-style-type: none"> <li>– Vertigo</li> <li>– Ear discomfort</li> </ul>
<b>Cardiac disorders</b>		<ul style="list-style-type: none"> <li>– Angina pectoris</li> <li>– Arrhythmia</li> <li>– Palpitations</li> </ul>
<b>Vascular disorders</b>	<ul style="list-style-type: none"> <li>– Flushing</li> </ul>	<ul style="list-style-type: none"> <li>– Embolism</li> <li>– Hypertension</li> <li>– Hypotension</li> </ul>
<b>Respiratory, thoracic and mediastinal disorders</b>	<ul style="list-style-type: none"> <li>– Dyspnoea</li> <li>– Cough</li> </ul>	<ul style="list-style-type: none"> <li>– Pulmonary embolism</li> <li>– Pleural effusion</li> <li>– Rhinorrhoea</li> <li>– Dysphonia</li> <li>– Oropharyngeal pain</li> <li>– Epistaxis</li> </ul>



<b>System Organ Class (MedDRA)<sup>a</sup></b>	<b>Common</b>	<b>Uncommon</b>
<b>Gastrointestinal disorders</b>	<ul style="list-style-type: none"> <li>– Abdominal pain</li> <li>– Constipation</li> <li>– Stomatitis</li> <li>– Oral disorder</li> </ul>	<ul style="list-style-type: none"> <li>– Enterocolitis haemorrhagic</li> <li>– Gastrointestinal haemorrhage</li> <li>– Pancreatitis acute</li> <li>– Ascites</li> <li>– Ileus</li> <li>– Subileus</li> <li>– Colitis</li> <li>– Gastritis</li> <li>– Reflux gastritis</li> <li>– Oesophagitis</li> <li>– Impaired gastric emptying</li> <li>– Abdominal distension</li> <li>– Anal inflammation</li> <li>– Mouth ulceration</li> <li>– Dyspepsia</li> <li>– Gastrooesophageal reflux disease</li> <li>– Proctalgia</li> <li>– Buccal polyp</li> <li>– Gingival bleeding</li> <li>– Glossitis</li> <li>– Periodontal disease</li> <li>– Tooth disorder</li> <li>– Retching</li> <li>– Flatulence</li> <li>– Breath odour</li> </ul>
<b>Hepatobiliary disorders</b>	<ul style="list-style-type: none"> <li>– Hyperbilirubinaemia</li> </ul>	<ul style="list-style-type: none"> <li>– Hepatotoxicity</li> <li>– Biliary dilatation</li> </ul>
<b>Skin and subcutaneous tissue disorders</b>	<ul style="list-style-type: none"> <li>– Palmar-plantar erythrodysesthesia syndrome<sup>c</sup></li> <li>– Rash</li> <li>– Alopecia</li> <li>– Pruritus</li> <li>– Dry skin</li> </ul>	<ul style="list-style-type: none"> <li>– Skin exfoliation</li> <li>– Urticaria</li> <li>– Photosensitivity reaction</li> <li>– Erythema</li> <li>– Acne</li> <li>– Hyperhidrosis</li> <li>– Blister</li> <li>– Nail Disorder</li> </ul>
<b>Musculoskeletal and connective tissue disorders</b>		<ul style="list-style-type: none"> <li>– Joint swelling</li> <li>– Arthralgia</li> <li>– Bone pain</li> <li>– Myalgia</li> <li>– Musculoskeletal pain</li> <li>– Muscular weakness</li> <li>– Muscle spasms</li> <li>– Pain in extremity</li> <li>– Sensation of heaviness</li> </ul>

<b>System Organ Class (MedDRA)<sup>a</sup></b>	<b>Common</b>	<b>Uncommon</b>
<b>Renal and urinary disorders</b>	<ul style="list-style-type: none"> <li>– Proteinuria</li> </ul>	<ul style="list-style-type: none"> <li>– Renal failure</li> <li>– Cystitis noninfective</li> <li>– Micturition disorder</li> <li>– Haematuria</li> <li>– Leukocyturia</li> </ul>
<b>Reproductive system and breast disorders</b>		<ul style="list-style-type: none"> <li>– Menstrual disorder</li> </ul>
<b>General disorders and administration site conditions</b>	<ul style="list-style-type: none"> <li>– Pyrexia</li> <li>– Oedema</li> <li>– Mucosal inflammation</li> <li>– Malaise</li> </ul>	<ul style="list-style-type: none"> <li>– General physical health deterioration</li> <li>– Pain</li> <li>– Feeling of body temperature change</li> <li>– Xerosis</li> </ul>
<b>Investigations</b>	<ul style="list-style-type: none"> <li>– Hepatic enzyme increased</li> <li>– Blood alkaline phosphatase increased</li> <li>– Weight decreased</li> </ul>	<ul style="list-style-type: none"> <li>– Blood creatinine increased</li> <li>– Electrocardiogram QT prolonged</li> <li>– International normalised ratio increased</li> <li>– Activated partial thromboplastin time prolonged</li> <li>– Blood urea increased</li> <li>– Blood lactate dehydrogenase increased</li> <li>– Protein total decreased</li> <li>– C-reactive protein increased</li> <li>– Haematocrit decreased</li> </ul>

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

b. Fatal cases have been reported.

c. Hand-foot skin reaction.

Rare and very rare events reported in the Phase III (RECOURSE) clinical trial could not be estimated from the available data due to the limited number of patients exposed to ORCANTAS.

#### *Elderly*

Patients aged ≥ 65 years who received ORCANTAS had a higher incidence of the following events compared to patients aged < 65 years: Grade 3 or 4 neutropenia (48% v 30%), Grade 3 anaemia (26% v 12%), Grade 3 or 4 leucopenia (26% v 18%) and Grade 3 or 4 thrombocytopenia (9% v 2%).

#### *Infections*

In the Phase III (RECOURSE) clinical trial, treatment-related infections occurred more frequently in ORCANTAS-treated patients (5.6%) compared to those receiving placebo (1.9%).

#### *Proteinuria*

In the RECOURSE clinical trial, treatment-related proteinuria occurred more frequently in ORCANTAS-treated patients (2.8%) compared to those receiving placebo (1.5%), all of which were Grade 1 or 2 in severity (see *PRECAUTIONS* section).

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*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 ORCANTAS-treated patients who received prior radiotherapy compared to those that did not.

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

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

**DOSAGE AND ADMINISTRATION**

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

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

Dose

The recommended starting dose of ORCANTAS in adults is 35 mg/m<sup>2</sup>/dose (based on the trifluridine component) administered orally twice daily on Days 1 to 5 and Days 8 to 12 of each 28-day cycle as long as benefit is observed or until unacceptable toxicity occurs (see *PRECAUTIONS* section).

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

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

Starting dose

**Table 5 – Starting dose calculation according to body surface area (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

Dose modification guidelines

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

A maximum of 3 dose reductions to a minimum dose of 20 mg/m<sup>2</sup> twice daily, are permitted. Dose escalation is not permitted after it has been reduced.

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In the event of haematological and/or non-haematological toxicities patients should follow the dose interruption, resumption and reduction criteria stated in Table 6, Table 7 and Table 8 below.

**Table 6 - Dose interruption and resumption criteria for haematological toxicities related to myelosuppression**

Parameter	Interruption criteria	Resumption criteria <sup>a</sup>
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 7 - Recommended dose modifications for ORCANTAS in case of haematological and non-haematological adverse reactions**

Adverse reaction	Recommended dose modifications
<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 anti-diarrhoeal 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 7).</li> <li>• Dose reductions are permitted to a minimum dose of 20 mg/m<sup>2</sup>/dose twice daily.</li> <li>• Do not increase dose after it has been reduced.</li> </ul>

\* Common terminology criteria for adverse events

**Table 8 - Dose reductions according to body surface area (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

#### *Paediatric population*

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

#### *Elderly patients*

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



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*Patients with impaired renal function*

*Mild renal impairment (CrCl 60 to 89 mL/min) or moderate renal impairment (CrCl 30 to 59 mL/min)*

No adjustment of the starting dose is recommended in patients with mild or moderate renal impairment (see *PRECAUTIONS* and *PHARMACOLOGY-Pharmacokinetics* sections).

Patients with moderate renal impairment (CrCl = 30 to 59 mL/min) at baseline had a higher incidence (defined as a difference of at least 5%) of  $\geq$  Grade 3 adverse events (AEs), serious AEs, and dose delays and reductions compared to the patients with normal (CrCl  $\geq$  90 mL/min) or mild renal impairment (CrCl = 60 to 89 mL/min) at baseline. In addition, a higher exposure of trifluridine and tipiracil was observed in patients with moderate renal impairment at baseline, compared with patients with normal renal function or patients with mild renal impairment at baseline (see *PHARMACOLOGY* section). Patients with moderate renal impairment should be more frequently monitored for haematological toxicities and may require dose adjustment (see *Dose modification guidelines* heading).

*Severe renal impairment (CrCl < 30 mL/min) or end stage renal disease*

Administration is not recommended in patients with severe renal impairment or end stage renal disease as there are no data available for these patients (see *PRECAUTIONS* section).

*Patients with impaired hepatic function*

*Mild hepatic impairment*

No adjustment of the starting dose is recommended in patients with mild hepatic impairment (see *PHARMACOLOGY-Pharmacokinetics* section).

*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 *PRECAUTIONS* and *PHARMACOLOGY-Pharmacokinetics* sections).

*Ethnicity*

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

Method of administration

ORCANTAS is for oral use. Take ORCANTAS with a glass of water, within one hour after completion of the morning and evening meals.

Special precautions for disposal

Hands should be washed after handling tablets.

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

**OVERDOSAGE**

Advice on overdose management can be obtained from the national Poisons Information Centre by telephoning 131126.

The highest dose of ORCANTAS administered was 180 mg/m<sup>2</sup> per day. The adverse events reported in association with an overdose were consistent with the established safety profile. The

**Attachment 1: Product information for AusPAR Lonsurf and Orcantas Servier Laboratories Australia Pty Ltd PM-2016-00929-1-4 Final 12 June 2018. This Product Information was approved at the time this AusPAR was published.**

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primary anticipated complication of an overdose is bone marrow suppression. There is no known antidote for an overdose of ORCANTAS.

If overdose occurs, supportive management is recommended.

**PRESENTATION AND STORAGE CONDITIONS**

Presentation

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

*ORCANTAS 15/6.14*

Each film-coated tablet contains trifluridine 15 mg and tipiracil hydrochloride 7.065 mg (equivalent to tipiracil 6.14 mg). The tablet is a white, biconvex, round, film-coated tablet, imprinted with '15' on one side, and '102' and '15 mg' on the other side, in grey ink.

*ORCANTAS 20/8.19*

Each film-coated tablet contains trifluridine 20 mg and tipiracil hydrochloride 9.420 mg (equivalent to tipiracil 8.19 mg). The tablet is a pale red, biconvex, round, film-coated tablet, imprinted with '20' on one side, and '102' and '20 mg' on the other side, in grey ink.

Storage conditions

Store below 30°C.

**NAME AND ADDRESS OF THE SPONSOR**

Servier Laboratories (Aust.) Pty Ltd

8 Cato Street

PO Box 196

Hawthorn, VIC 3122

**POISONS SCHEDULE OF THE MEDICINE**

S4 - Prescription Only Medicine

**DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)**

23 May 2017

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<sup>#</sup> The 60 tablet pack size is not distributed in Australia