Part VI: Summary of the risk management plan

Summary of risk management plan for Lonsurf (trifluridine and tipiracil)

This is a summary of the risk management plan (RMP) for Lonsurf. The RMP details important risks of Lonsurf, how these risks can be minimised, and how more information will be obtained about Lonsurf's risks and uncertainties (missing information).

Lonsurf's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Lonsurf should be used.

This summary of the RMP for Lonsurf should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Lonsurf 's RMP.

I. The medicine and what it is used for

Lonsurf is authorised 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, 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 and 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 SmPC for the full indication). It contains trifluridine and tipiracil (as hydrochloride) as the active substances and it is given by oral administration.

Further information about the evaluation of Lonsurf's benefits can be found in Lonsurf's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/lonsurf

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Lonsurf, together with measures to minimise such risks and the proposed studies for learning more about Lonsurf's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;

- Important advice on the medicine's packaging;
- The authorised pack size – the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status – the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

If important information that may affect the safe use of Lonsurf is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Lonsurf are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Lonsurf. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long- term use of the medicine).

List of important risks and missing information	
Important identified risks	Safety in patients with moderate or severe renal impairment
Important potential risks	Developmental toxicity/Use in pregnant women
Missing information	Use in patients in a worse condition than ECOG 0-1.

II.B Summary of important risks

Important Identified Risk: Safety in patients with moderate or severe renal impairment	
Evidence for linking the risk to the medicine	**Clinical data**: Based on a population PK analysis, the exposure of Lonsurf in patients with mild renal impairment (CLcr= 60 to 89 mL/min) was similar to those in patients with normal renal function (CLcr ≥ 90 mL/min). A higher exposure of Lonsurf was observed in moderate renal impairment (CLcr = 30 to 59 mL/min). Estimated (CLcr)

Important Identified Risk: Safety in patients with moderate or severe renal impairment	
	was a significant covariate for Oral clearance (CL/F) in both final models of trifluridine and tipiracil hydrochloride. The mean relative ratio of Area Under the Curve (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. During mCRC clinical development it has been shown that patients with moderate renal impairment at baseline had a higher incidence of ≥ Grade 3 Aes and serious Aes, and dose delays and reductions compared to patients with normal renal function or mild renal impairment. In mGC clinical development there was no marked difference between the normal renal function, the mild and the moderate renal impairment subgroups (based on baseline CLcr) with respect to overall incidence of Aes, ≥ Grade 3 Aes or serious Aes, dose delays and reductions. However, several of the most frequently reported Aes increased with the degree of renal impairment (anaemia, neutropenia, decreased appetite and diarrhoea) and patients with moderate impairment had higher incidences of Grade 3 and 4 abnormalities for haemoglobin and leukocytes compared to normal and mild impairment subgroups. In a dedicated phase 1, open-label study conducted to evaluate the safety, tolerability, and pharmacokinetics of trifluridine-tipiracil in patients with advanced solid tumors and varying degrees of renal impairment (TO-TAS-102-107), based on PK and safety data from the normal renal function, mild and moderate renal impairment cohorts, a lower starting dose was selected for the severe renal impairment cohort (dose of 20 mg/m2 BID) and one dose reduction was allowed to 15 mg/m2 BID in case of toxicities requiring a dose reduction. Renal function impairment had no significant effect on Cmax and AUCs of trifluridine following multiple administration of trifluridine-tipiracil, although tipiracil hydrochloride exposure was increased in patients with renal impairment. Consistent with current knowledge on safety profile of trifluridine-tipiracil moderate renal impairment patients tended to show a higher incidence of ≥ Grade 3 adverse events and serious adverse events were more frequent in mild and moderate renal impairment patients compared to normal renal function cohort. However, the

Important Identified Risk: Safety in patients with moderate or severe renal impairment	
	safety profile in patients with severe renal impairment who received 20 mg/m2/dose twice daily did not show important changes compared to normal renal function and mild renal impairment cohorts demonstrating that a dose of 20 mg/m2 twice daily is appropriate and tolerable for this population of patients. Patients with end stage renal disease (CLcr <15 mL/min or patients requiring dialysis) were not enrolled in the study.
Risk factors and risk groups	Not applicable
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.2 , 4.4 Legal status: Prescription only medicine. Lonsurf should only be prescribed by a qualified physician experienced in treating cancer patients with anti-neoplastic medicinal products. Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

Important Potential Risk: Developmental toxicity/ Use in pregnant women	
Evidence for linking the risk to the medicine	**Non-clinical data**: Based on finding in animals, 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. Pregnancy, women of childbearing potential without contraception were not enrolled in the clinical development of Lonsurf.
Risk factors and risk groups	Not applicable
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.6 PL section 2 Legal status: Prescription only medicine. Lonsurf should only be prescribed by a qualified physician experienced in treating cancer patients with anti-neoplastic medicinal products. Additional risk minimisation measures: None

Missing information: Use in patients in a worse condition than ECOG 0-1	
Risk minimisation measures	No risk minimisation measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study DIM-95005-001 (PROMETCO)

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Lonsurf.

II.C.2 Other studies in post-authorisation development plan

DIM-95005-001 (PROMETCO) – A Real World Evidence Prospective Cohort Study in the Management of Metastatic Colorectal Cancer: A Clinical and Patient Perspective

Purpose of the study:

Rational: The use of Lonsurf in cancer patients with an ECOG performance status of ≥2 has not been studied.

Study objectives: To provide real world data on treatment patterns, associated effectiveness and safety, and impact on patients with mCRC after two disease progressions. The study might further characterise the safety profile of Lonsurf with respect to the area of missing information "Use in patients in worse condition than ECOG 0-1".