PDL DRUG REVIEW

Proprietary Name: Lonsurf®
Common Name: trifluridine & tipiracil
PDL Category: Antineoplastics

Comparable Products	Preferred Drug List Status
Stivarga	Non-Recommended with Conditions

Summary

Pharmacology/Usage: Lonsurf® is a combination agent that consists of an antineoplastic thymidine-based nucleoside analogue (trifluridine) and a thymidine phosphorylase inhibitor (tipiracil). The addition of tipiracil increases trifluridine exposure by inhibiting its metabolism by thymidine phosphorylase. When trifluridine enters into cancer cells, it is incorporated into DNA, interferes with DNA synthesis and inhibits cell proliferation. In mice, this product has shown anti-tumor activity against KRAS wild-type and mutant human colorectal cancer xenografts.

Indication: For the treatment of patients with metastatic colorectal cancer who have been previously treated with fluoropyrimidine, oxaliplatin, and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy.

There was no pregnancy category provided for this product; however, the risk summary indicates that based on animal data and its mechanism of action Lonsurf® can cause fetal harm. Use caused embryo-fetal lethality and embryo-fetal toxicity in pregnant rats when given during gestation. There was no data on exposure in pregnant woman. It is recommended to advise women of the potential risk to a fetus. Females of reproductive potential should be advised to use effective contraception during treatment, and males with female partners of reproductive potential should be advised to use condoms during treatment and for at least 3 months after the final dose. The safety and efficacy of use in the pediatric population have not been established.

Dosage Forms: Film-coated tablets containing trifluridine/tipiracil: 15/6.14mg and 20/8.19mg

Recommended Dosage: The recommended starting dose of Lonsurf® is 35mg/m^2 up to a maximum of 80mg per dose (based on trifluridine) PO BID within one hour of completion of morning and evening meals on days 1 through 5 and days 8 through 12 of each 28-day cycle. Take until disease progression or unacceptable toxicity.

A complete blood cell count should be obtained prior to and on day 15 of each cycle. *The cycle of Lonsurf® should not be started until*: absolute neutrophil count (ANC) is ≥1500/mm^3 or febrile neutropenia is resolved; platelets are ≥75,000/mm^3; and Grade 3 or 4 non-hematological adverse reactions are resolved to Grade 0 or 1. *Within a treatment cycle, withhold Lonsurf® for any of the following*: ANC <500/mm^3 or febrile neutropenia; platelets <50,000/mm^3; Grade 3 or 4 non-hematological adverse reactions. *After recovery, resume Lonsurf® after reducing*

the dose by 5mg/m^2/dose from the previous dose level, if the following occur: febrile neutropenia; uncomplicated Grade 4 neutropenia or thrombocytopenia that results in >1 week delay in start of next cycle; or non-hematologic Grade 3 or Grade 4 adverse reaction except for Grade 3 nausea and/or vomiting controlled by anti-emetic therapy or Grade 3 diarrhea responsive to antidiarrheal medication.

A maximum of 3 dose reductions are allowed to a minimum of 20mg/m^2 BID. Do not escalate the Lonsurf® dose after it has been reduced.

There are no recommended dose adjustments to the starting dose of Lonsurf® in patients with mild or moderate renal impairment; however, patients with moderate renal impairment may require dose modification for increased toxicity. There were no patients enrolled in the study with severe renal impairment. There are no recommended dose adjustments for patients with mild hepatic; however, patients with moderate or severe hepatic impairment were not enrolled in the study.

Drug Interactions: Drug interaction studies were not performed.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Lonsurf®) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence of the active drug was the same as or less than placebo.* The most frequently reported adverse events included nausea (24%), diarrhea (20%), vomiting (14%), abdominal pain (3%), stomatitis (2%), asthenia /fatigue (17%), pyrexia (5%), decreased appetite (10%), dysgeusia (5%), infections (12%), pulmonary emboli (2%), and alopecia (6%). The most frequently reported infections were nasopharyngitis (2%) and urinary tract infections (2%). Lab abnormalities include anemia (44%), neutropenia (66%), and thrombocytopenia (34%).

Severe and life-threatening myelosuppression (Grade 3-4) were reported during Lonsurf® treatment in a clinical trial. It is recommended to obtain complete blood counts prior to and on day 15 of Lonsurf® treatment, as well as when clinically indicated.

Contraindications: There are currently no contraindications listed with this product.

Manufacturer: Taiho Pharmaceuticals

Analysis: The safety and efficacy of Lonsurf® were established in a randomized, double-blind, placebo-controlled study that included patients (N=800) with previously treated metastatic colorectal cancer and who were randomized to Lonsurf® plus best supportive care (BSC) or placebo plus BSC until disease progression or unacceptable toxicity. The main eligibility criteria included prior treatment with ≥2 lines of standard chemotherapy, absence of brain metastasis, and absence of ascites requiring drainage in the past 4 weeks. The main efficacy outcome was overall survival (OS), with an additional efficacy outcome of progression-free survival (PFS).

Results suggested that there was a statistically significant improvement in OS and PFS in patients receiving Lonsurf® as compared to patients receiving placebo. Please refer to the table below for specific results, which was adapted from the prescribing information.

Efficacy Outcome	Lonsurf®	Placebo
OS		
Number of deaths, N (%)	364 (68%)	210 (79%)
Median OS, months	7.1	5.3
Hazard ratio & p-value	0.68; p<0.001	
PFS		
Number of Progression or Death, N (%)	472 (88%)	251 (94%)
Hazard ratio & p-value	0.47; p<0.001	

Place in Therapy: Lonsurf®, FDA approved for the treatment of patients with metastatic colorectal cancer who have been previously treated, was found to be significantly more effective as compared to placebo for improving overall survival and progression-free survival in patients with metastatic colorectal cancer.

It is recommended that Lonsurf® require clinical prior authorization to verify diagnosis and a prior trial with fluoropyrimidine, oxaliplatin, and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy.

PDL Placement: ☐ **Recommended**
☒ **Non-Recommended with Conditions**

References

[1] Lonsurf [package insert]. Princeton, NJ: Taiho Oncology, Inc; 2015.