MEDISON

We are **Always Ahead** | We **Grow as One** | We **Care**

אוקטובר 2024

רופא/ה נכבד/ה
רוקח/ת נכבד/ה,

חברת מדיסון פארמה בע"מ שמחה להודיעכם על אישור משרד הבריאות לתוספת ההתוויה עבור התכשיר:

**Lonsurf 15 mg/6.14 mg** **לונסורף 15 מ"ג/6.14 מ"ג**
**Lonsurf 20 mg/8.19 mg** **לונסורף 20 מ"ג/8.19 מ"ג**

**טבליות מצופות**

**מרכיבים פעילים** : tipiracil (as hydrochloride), trifluridine

**התוויות מאושרות (ההתוויה החדשה מסומנת בצהוב):**

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.

LONSURF in combination with bevacizumab, is indicated for the treatment of adult patients with metastatic colorectal cancer previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy.

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.

להלן העדכונים בעלון לרופא המהווים החמרות (מסומנים בצהוב):

**4.2 Posology and method of administration**

Posology

The recommended starting dose of Lonsurf in adults, as monotherapy or in combination with bevacizumab, 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 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.
[…]

**4.4 Special warnings and precautions for use**

Bone marrow suppression

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[…] 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.

[…]

## 4.6 Fertility, pregnancy and lactation

[…]
Fertility
[…]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.
[…]

## 4.8 Undesirable effects

Summary of safety profile

[…]

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 (≥ 30%) are neutropenia (69% [48% ≥ Grade 3]), fatigue (35% [3% ≥ Grade 3]), and nausea (33% [1% ≥ Grade 3]).

The most common adverse reactions (≥ 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%).

[…]

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.

[…]

**Table 5 - Adverse reactions reported in clinical studies in patients treated with Lonsurf**

| System Organ Class (MedDRA)[a] | Adverse reactions | Frequency | |
|---|---|---|---|
| | | Monotherapy | Combination with bevacizumab |
| Infections and infestations | | […] | |
| | infection | Uncommon | Common |
| | Urinary tract infection | Uncommon | Uncommon |
| | […] | | |
| | Gingivitis | Rare | Uncommon |
| | [...] | | |
| […] | | | |
| Blood and lymphatic system disorders | Anaemia | Very common | Very common |
| | Neutropenia | Very common | Very common |
| | Leukopenia | Very common | Common |
| | Thrombocytopenia | Very common | Very common |
| | Febrile neutropenia | Common | Uncommon |
| | Lymphopenia | Common | Common |
| | Pancytopenia | Uncommon | Uncommon |
| | […] | | |
| Metabolism and nutrition disorders | Decreased appetite | Very common | Very common |
| | Hypoalbuminaemia | Common | Uncommon |
| | […] | | |
| | Hyperglycaemia | Uncommon | Uncommon |
| | […] | | |
| […] | | | |
| Nervous system disorders | Dysgeusia | Common | Common |
| | Dizziness | Uncommon | Common |
| | Headache | Uncommon | Common |
| | Neuropathy peripheral | Uncommon | Uncommon |
| | Paraesthesia | Uncommon | Uncommon |
| | […] | | |
| […] | | | |
| Vascular disorders | Hypertension | Uncommon | Common |
| | […] | | |
| Respiratory, thoracic and mediastinal disorders | Dyspnoea | Common | Common |
| | […] | | |
| | Dysphonia | Uncommon | Uncommon |
| | […] | | |
| | Rhinorrhoea | Rare | Uncommon |
| | […] | | |

| System Organ Class (MedDRA)[a] | Adverse reactions | Frequency | |
|---|---|---|---|
| | | Monotherapy | Combination with bevacizumab |
| 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 |
| | | […] | |
| | 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 |
| | | […] | |
| Hepatobiliary disorders | Hyperbilirubinaemia | Common | Common |
| | | […] | |
| Skin and subcutaneous tissue disorders | Alopecia | Common | Common |
| | Dry skin | Common | Common |
| | Pruritus | Common | Uncommon |
| | Rash | Common | Uncommon |
| | Nail disorder | Uncommon | Uncommon |
| | Palmar-plantar erythrodysaesthesia syndrome[c] | Uncommon | Uncommon |
| | | […] | |
| Musculoskeletal and connective tissue disorders | Arthralgia | Uncommon | Common |
| | Myalgia | Uncommon | Common |
| | Muscular weakness | Uncommon | Uncommon |
| | Pain in extremity | Uncommon | Uncommon |
| | | […] | |
| | Limb discomfort | Uncommon | - |
| | | […] | |
| Renal and urinary disorders | Proteinuria | Common | Uncommon |
| | | […] | |
| Reproductive system and breast disorders | Menstrual disorder | Rare | Uncommon |

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| System Organ Class (MedDRA)[a] | Adverse reactions | Frequency | |
|---|---|---|---|
| | | Monotherapy | Combination with bevacizumab |
| General disorders and administration site conditions | Fatigue | Very common | Very common |
| | Pyrexia | Common | Uncommon |
| | Mucosal inflammation | Common | Uncommon |
| | […] | | |
| | Pain | Uncommon | Uncommon |
| | […] | | |
| Investigations | Weight decreased | Common | Common |
| | Hepatic enzyme increased | Common | Common |
| | Blood alkaline phosphatase increased | Common | Uncommon |
| | […] | | |

[…]

Elderly

Patients 65 years of age or older who received Lonsurf as monotherapy had a higher incidence (≥ 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 (≥ 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 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 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

[…] 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%).

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להלן העדכונים בעלון לצרכן המהווים החמרות (מסומנים בצהוב):

**2. <u>לפני שימוש בתרופה</u>**

[...] <u>פוריות</u>

לונסורף עלולה להשפיע על יכולתך להביא תינוק לעולם. יש לשוחח על כך עם הרופא לפני נטילת התרופה. [...]

**4. <u>תופעות לוואי</u>**

[...]

**תופעות לוואי שכיחות מאוד: עלולות להשפיע על יותר מ- 1 מתוך 10 אנשים:**

[...]

- נפיחות ברקמות הריריות בפה

[...]

**תופעות לוואי שכיחות: עלולות להשפיע על עד 1 מתוך 10 אנשים:**

[...]

- תחושת קוצר נשימה, זיהומים בחזה, בדרכי הנשימה או בריאות
- זיהום ויראלי
- כאב במפרקים
- תחושת סחרחורת, כאב ראש
- לחץ דם גבוה
- כיבים בפה
- כאב שרירים

[...]

העלון לרופא והעלון לצרכן נמצאים בקישור, וכן מפורסמים במאגר התרופות שבאתר משרד הבריאות, וניתן לקבלם מודפסים על ידי פניה לבעל הרישום.

בברכה,

מדיסון פארמה בע"מ

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