MEDISON

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

נובמבר 2024

רופא/ה נכבד/ה
רוקח/ת נכבד/ה,

הריני להודיעכם על שינוי במשטר המינון במטופלים עם תפקוד כליות לקוי של התכשירים הבאים:

| | |
|---|---|
| **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 :**

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 המתייחסים לשינוי משטר המינון במטופלים עם תפקוד כליות לקוי:

**4.2 Posology and method of administration**

[…]

**Table 3 - Recommended dose modifications for Lonsurf in case of haematological and non-haematological adverse reactions**

| Adverse reaction | Recommended dose modifications |
|---|---|
| • Febrile neutropenia<br>• 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<br>• 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 | • Interrupt dosing until toxicity resolves to Grade 1 or baseline.<br>• When resuming dosing, decrease the dose level by 5 mg/m$^2$/dose from the previous dose level (Table 4).<br>• 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.<br>• Do not increase dose after it has |

**Medison Pharma Ltd.**
10 Hashiloach St., P.O.B 7090, Petach-Tikva 4917002 Israel
Tel. +972. 3. 925. 0250, Fax. +972. 3. 922. 5740
medisonpharma.com

| Adverse reaction | Recommended dose modifications |
|---|---|
| medicinal products | been reduced. |

[…]

Special populations

[…]

- *Severe renal impairment (CrCl ~~below 30~~15 to 29 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 section 4.4).~~

  For patients with severe renal impairment a starting dose of 20 mg/m$^2$ twice daily is recommended (see section 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 no-haemtological 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 BSA**

| Reduced dose | | BSA (m$^2$) | 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** | | | | | |
| **20 mg/m$^2$** | | < 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/m$^2$ to 15 mg/m$^2$** | | | | | |
| **15 mg/m$^2$** | | < 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).

[…]

**4.4 Special warnings and precautions for use**

[…]

Renal impairment

Lonsurf is not recommended for use in patients with ~~severe renal impairment or~~ end-stage renal disease (creatinine clearance [CrCl] < ~~30~~15 mL/min or requiring dialysis~~, respectively~~), as Lonsurf has not been studied in these patients (see section 5.2).
The global incidence of adverse events (AEs) is similar in normal renal function (CrCl ≥ 90 mL/min), mild (CrCl = 60 to 89 mL/min) or moderate (CrCl = 30 to 59 mL/min) renal impairment subgroups. However, the incidence of serious, severe AEs and AEs leading to dose modification tends to increase with advancing levels of renal impairment. In addition, a higher exposure of trifluridine and tipiracil hydrochloride was observed in patients with moderate renal impairment, compared with patients with normal renal function or patients with mild renal impairment (see section 5.2).
Patients with severe renal impairment (CrCl = 15 to 29 mL/min) and adjusted starting dose of 20 mg/m$^2$ twice daily had a safety profile consistent with the safety profile of Lonsurf in patients with normal renal function or mild renal impairment. Their exposure to trifluridine was similar to that of patients with normal renal function and their exposure to tipiracil hydrochloride was increased compared to patients with normal renal function, mild and moderate renal impairment (see sections 4.2 and 5.2).
Patients with renal impairment should be monitored closely when being treated with Lonsurf; patients with moderate or severe renal impairment should be more frequently monitored for haematological toxicities.

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

**Medison Pharma Ltd.**
10 Hashiloach St., P.O.B 7090, Petach-Tikva 4917002 Israel
Tel. +972. 3. 925. 0250, Fax. +972. 3. 922. 5740
medisonpharma.com