# הודעה על החמרה ( מידע בטיחות)

**תאריך09.05.2013**

**שם תכשיר באנגלית Alimta 100mg, 500mg**

**מספר רישום:.00/01 138 86 31721, 131 45 31049**

**שם בעל הרישום:Eli Lilly Israel Ltd.**

בעלון לרופא

|  |  |  |
| --- | --- | --- |
| **ההחמרות המבוקשות** | | |
| **פרק בעלון** | **טקסט נוכחי** | **טקסט חדש** |
| 4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION | In the absence of data regarding potential interaction with NSAIDs having longer half-lives such as piroxicam or rofecoxib, the concomitant administration with pemetrexed in patients with mild to moderate renal insufficiency should be interrupted for at least 5 days prior to, on the day of, and at least 2 days following pemetrexed administration (see section 4.4). | In the absence of data regarding potential interaction with NSAIDs having longer half-lives such as piroxicam or rofecoxib, the concomitant administration with pemetrexed in patients with mild to moderate renal insufficiency should be interrupted for at least 5 days prior to, on the day of, and at least 2 days following pemetrexed administration (see section 4.4). If concomitant administration of NSAIDs is necessary, patients should be monitored closely for toxicity, especially myelosuppression and gastrointestinal toxicity. |
| 4.8 UNDESIRABLE EFFECTS | **Tabulated list of adverse reactions** (page 14) | **Tabulated list of adverse reactions** (page 14)  \*\*See below attached revised (New) Table on page 14 in which the adverse events, *edema* and *renal disorders* have been moved into the table from their location on the following page and the frequency of many of the Adverse Events was updated.  Also, a footnote was added defining “*renal disorders*”. |
| 4. 8 UNDESIRABLE EFFECTS | Safety was assessed for patients who were randomised to receive pemetrexed (N=800). The incidence of adverse reactions was evaluated for patients who received ≤ 6 cycles of pemetrexed maintenance (N=~~568~~), and compared to patients who received > 6 cycles of pemetrexed (N=~~232~~). Increases in adverse reactions (all grades) were observed with longer exposure; ~~however, no~~. statistically significant differences in any individual Grade 3/4/5 adverse reactions were seen. | Safety was assessed for patients who were randomised to receive pemetrexed (N=800). The incidence of adverse reactions was evaluated for patients who received ≤ 6 cycles of pemetrexed maintenance (N=~~568~~519), and compared to patients who received > 6 cycles of pemetrexed (N=~~232~~281). Increases in adverse reactions (all grades) were observed with longer exposure; ~~however, no~~ A significant increase in the incidence of possibly study-drug-related Grade 3/4 neutropenia was observed with longer exposure to pemetrexed (≤6 cycles: 3.3%, > 6cycles: 6.4%: p=0.046). No statistically significant differences in any other individual Grade 3/4/5 adverse reactions were seen with longer exposure. |
| 4. 8 UNDESIRABLE EFFECTS | Rare cases of bullous conditions have been reported including Stevens-Johnson syndrome and Toxic epidermal necrolysis which in some cases were fatal.  Rarely, haemolytic anaemia has been reported in patients treated with pemetrexed. | Rare cases of bullous conditions have been reported including Stevens-Johnson syndrome and Toxic epidermal necrolysis which in some cases were fatal.  Rarely, haemolytic anaemia has been reported in patients treated with pemetrexed.  Rare cases of anaphylactic shock have been reported. |

**4.8 Undesirable Effects**

**Current Table on page 14:**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **System organ class** | **Frequency\*** | **Event\*\*** | **Pemetrexed\*\*\***  **(N =800)** | | **Placebo\*\*\***  **(N =402)** | |
| **All grades toxicity  (%)** | **Grade 3 - 4 toxicity**  **(%)** | **All grades toxicity**  **(%)** | **Grade 3 - 4 toxicity**  **(%)** |
| Blood and lymphatic system disorders | Very common | Hemoglobin  decreased | ~~14.6~~ | ~~3.5~~ | ~~4.7~~ | 0.5 |
| Common | Leukocytes  decreased | ~~4.9~~ | ~~1.6~~ | 0.7 | 0.2 |
| Neutrophils  decreased | ~~6.9~~ | ~~3.3~~ | 0.2 | 0.0 |
| Nervous system disorders | Common | Neuropathy-sensory | ~~6.1~~ | ~~0.5~~ | ~~4.5~~ | 0.2 |
| Gastrointestinal disorders | Very common | Nausea | ~~15.1~~ | ~~0.6~~ | 4.0 | 0.2 |
| Anorexia | ~~11.9~~ | 1.1 | 3.2 | 0.0 |
| Common | Vomiting | ~~7.4~~ | ~~0.1~~ | 1.5 | 0.0 |
| Mucositis/ stomatitis | ~~6.0~~ | ~~0.5~~ | 1.7 | 0.0 |
| Hepatobiliary disorders | Common | ALT (SGPT) elevation | ~~6.3~~ | 0.1 | 2.2 | 0.0 |
| AST (SGOT) elevation | ~~5.4~~ | 0.0 | 1.7 | 0.0 |
| Skin and subcutaneous tissue disorders | Common | Rash/ desquamation | ~~7.6~~ | 0.1 | ~~3.2~~ | 0.0 |
| General disorders and administration site conditions | Very common | Fatigue | ~~20.8~~ | ~~4.6~~ | ~~10.4~~ | ~~0.5~~ |
| Common | Pain | ~~6.6~~ | ~~0.6~~ | ~~4.2~~ | 0.0 |

Abbreviations: ALT = alanine ~~transaminase~~; AST = aspartate ~~transaminase~~; CTCAE = Common Terminology Criteria for Adverse Event; NCI = National Cancer Institute; SGOT = serum glutamic oxaloacectic ~~transaminase~~; SGPT = serum glutamic pyruvic ~~transaminase~~.

\* Definition of frequency terms: Very common - ≥ 10%; Common - > 5% and < 10%. For the purpose of this table, a cutoff of 5% was used for inclusion of all events where the reporter considered a possible relationship to pemetrexed.

\*\* Refer to NCI CTCAE Criteria (Version 3.0; NCI 2003) for each grade of toxicity. The reporting rates shown are according to CTCAE version 3.0.

\*\*\* Integrated adverse reactions table combines the results of the JMEN pemetrexed maintenance (N=663) and PARAMOUNT continuation pemetrexed maintenance (N=539) studies.

**Revised (New) Table on page 14**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **System organ class** | **Frequency\*** | **Event\*\*** | **Pemetrexed\*\*\***  **(N =800)** | | **Placebo\*\*\***  **(N =402)** | |
| **All grades toxicity  (%)** | **Grade 3 - 4 toxicity**  **(%)** | **All grades toxicity**  **(%)** | **Grade 3 - 4 toxicity**  **(%)** |
| Blood and lymphatic system disorders | Very common | Hemoglobin  decreased | 18.0 | 4.5 | 5.2 | 0.5 |
| Common | Leukocytes  decreased | 5.8 | 1.9 | 0.7 | 0.2 |
| Neutrophils  decreased | 8.4 | 4.4 | 0.2 | 0.0 |
| Nervous system disorders | Common | Neuropathy-sensory | 7.4 | 0.6 | 5.0 | 0.2 |
| Gastrointestinal disorders | Very common | Nausea | 17.3 | 0.8 | 4.0 | 0.2 |
| Anorexia | 12.8 | 1.1 | 3.2 | 0.0 |
| Common | Vomiting | 8.4 | 0.3 | 1.5 | 0.0 |
| Mucositis/ stomatitis | 6.8 | 0.8 | 1.7 | 0.0 |
| Hepatobiliary disorders | Common | ALT (SGPT) elevation | 6.5 | 0.1 | 2.2 | 0.0 |
| AST (SGOT) elevation | 5.9 | 0.0 | 1.7 | 0.0 |
| Skin and subcutaneous tissue disorders | common | Rash/ desquamation | 8.1 | 0.1 | 3.7 | 0.0 |
| General disorders and administration site conditions | Very common | Fatigue | 24.1 | 5.3 | 10.9 | 0.7 |
| Common | Pain | 7.6 | 0.9 | 4.5 | 0.0 |
| Edema | 5.6 | 0.0 | 1.5 | 0.0 |
| Renal Disorder | Common | Renal disorder\*\*\*\* | 7.6 | 0.9 | 1.7 | 0.0 |

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Event; NCI = National Cancer Institute; SGOT = serum glutamic oxaloacectic aminotransferase; SGPT = serum glutamic pyruvic aminotransferase.

\* Definition of frequency terms: Very common - ≥ 10%; Common - > 5% and < 10%. For the purpose of this table, a cutoff of 5% was used for inclusion of all events where the reporter considered a possible relationship to pemetrexed.

\*\* Refer to NCI CTCAE Criteria (Version 3.0; NCI 2003) for each grade of toxicity. The reporting rates shown are according to CTCAE version 3.0.

\*\*\* Integrated adverse reactions table combines the results of the JMEN pemetrexed maintenance (N=663) and PARAMOUNT continuation pemetrexed maintenance (N=539) studies.

\*\*\*\* Combined term includes increased serum/blood creatinine, decreased glomerular filtration rate, renal failure and renal/genitourinary- other.

**מצ"ב העלון, שבו מסומנות ההחמרות המבוקשות על רקע צהוב.**

שינויים שאינם בגדר החמרות סומנו (בעלון) **בטקסט אפור**