# 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

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| **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 | Hemoglobindecreased | ~~14.6~~ | ~~3.5~~ | ~~4.7~~ | 0.5 |
| Common | Leukocytesdecreased  | ~~4.9~~ | ~~1.6~~ | 0.7 | 0.2 |
| Neutrophilsdecreased  | ~~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 subcutaneoustissue 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 | Hemoglobindecreased | 18.0 | 4.5 | 5.2 | 0.5 |
| Common | Leukocytesdecreased  | 5.8 | 1.9 | 0.7 | 0.2 |
| Neutrophilsdecreased  | 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 subcutaneoustissue 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**