הודעה על החמרה (מידע בטיחות)

תאריך 09.05.2013

שם תכשיר באנגלית Alimta 100mg, 500mg

מספר רישום: 138 86 31721, 131 45 3104900/01.

שם בעל הרישום: Eli Lilly Israel Ltd.

בעלון לרופא

ההחמרות המבוקשות		
טקסט חדש	**טקסט נוכחי**	**פרק בעלון**
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.	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).	**4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION**
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*".	**Tabulated list of adverse reactions** (page 14)	**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~~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.	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.	**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 anaphylactic shock have been reported.	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.	**4. 8 UNDESIRABLE EFFECTS**

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**