הודעה על החמרה (מידע בטיחות)

תאריך: 02.05.2012

שם תכשיר Alimta 100mg, 500mg

מספר רישום: 138 86 31721, 131 45 31049

שם בעל הרישום: Eli Lilly Israel Ltd.

השינויים בעלון מסומנים על רקע צהוב

בעלון לרופא

פרטים על השינוי/ים המבוקש/ים		
טקסט חדש	**טקסט נוכחי**	**פרק בעלון**
Malignant pleural mesothelioma ALIMTA in combination with cisplatin is indicated for the treatment of patients with malignant pleural mesothelioma whose disease is unresectable or who are otherwise not candidates for curatible surgery. Non-small cell lung cancer: ALIMTA in combination with cisplatin is indicated for the first line treatment of patients with locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology (see section 5.1). ALIMTA is indicated as monotherapy for the maintenance treatment of locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology in patients whose disease has not progressed immediately following platinum-based chemotherapy (see section 5.1). ALIMTA is indicated as monotherapy for the second line treatment of patients with locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology (see section 5.1).	Malignant pleural mesothelioma ALIMTA in combination with cisplatin is indicated for the treatment of patients with malignant pleural mesothelioma whose disease is unresectable or who are otherwise not candidates for curatible surgery. Non-small cell lung cancer: ALIMTA in combination with cisplatin is indicated for the first line treatment of patients with locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology (see section 5.1). ALIMTA is indicated as monotherapy for the second line treatment of patients with locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology (see section 5.1).	**4.1THERAPEUTIC INDICATIONS**
Tabulated list of adverse reactions (page 13) The table below provides the frequency and severity of undesirable effects considered possibly related to study drug that have been reported in > 5% of 800 patients randomly assigned to receive single agent pemetrexed and 402 patients randomly assigned to receive placebo in the single-agent pemetrexed maintenance (JMEN: N= 663) and continuation pemetrexed maintenance (PARAMOUNT: N=539) studies. All patients were diagnosed with Stage IIIB or IV NSCLC and had received prior platinum-	**Tabulated list of adverse reactions** (page 13) The table below provides the frequency and severity of undesirable effects considered possibly related to study drug that have been reported in > 5% of ~~441~~ patients randomly assigned to receive single agent pemetrexed and ~~222~~ patients randomly assigned to receive placebo in the single-agent maintenance ~~pemetrexed study (Study~~ JMEN~~)~~. All patients were diagnosed with Stage IIIB or IV NSCLC and had received prior platinum-based chemotherapy. Patients in both study arms were fully supplemented	**4.8 UNDESIRABLE EFFECTS**

based chemotherapy. Patients in both study arms were fully supplemented with folic acid and vitamin B_{12}.	with folic acid and vitamin B_{12}.	
**See below attached revised (New) Table on page 14 in which the adverse events, "Infection" and "Diarrhea" were removed and the frequency of many of the Adverse Events was updated.	**See below attached current Table on page 14:	**4. 8 UNDESIRABLE EFFECTS**
Foot notes of Table on page 14 * 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.	Foot notes of Table on page 14 * 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.	**4. 8 UNDESIRABLE EFFECTS**
Page 14-15 Clinically relevant CTC toxicity of any grade that was reported in ≥ 1% and ≤ 5% of the patients that were randomly assigned to pemetrexed include: febrile neutropenia, infection, decreased platelets, decreased creatinine, clearancediarrhoea constipation, edema, alopecia, increased creatinine, pruritis/itching, fever (in the absence of neutropenia), ocular surface disease (including conjunctivitis), increased lacrimation, decreased glomerular filtration rate, dizziness and motor neuropathy. Clinically relevant CTC toxicity that was reported in < 1% of the patients that were randomly assigned to pemetrexed include: allergic reaction/hypersensitivity, erythema multiforme, renal failure, supraventricular arrhythmia and pulmonary embolism. 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.	Page 14-15 Clinically relevant CTC toxicity of any grade that was reported in ≥ 1% and ≤ 5% of the patients that were randomly assigned to pemetrexed include: decreased platelets, decreased creatinine clearance, constipation, edema, alopecia, increased creatinine, pruritis/itching, fever (in the absence of neutropenia), ocular surface disease (including conjunctivitis), increased lacrimation, ~~and~~ decreased glomerular filtration rate. Clinically relevant CTC toxicity that was reported in < 1% of the patients that were randomly assigned to pemetrexed include: ~~febrile neutropenia,~~ allergic reaction/hypersensitivity, ~~motor neuropathy~~, erythema multiforme, renal failure, ~~and~~ supraventricular arrhythmia. The incidence of adverse reactions was evaluated for patients who received ≤ 6 cycles of pemetrexed, and compared to patients who received > 6 cycles of pemetrexed. Increases in adverse reactions (all grades) were observed with longer exposure; however, no statistically significant differences in Grade 3/4 adverse reactions were seen.	**4. 8 UNDESIRABLE EFFECTS**

PARAMOUNT A multicentre, randomised, double-blind, placebo-controlled Phase 3 study (PARAMOUNT), compared the efficacy and safety of continuation maintenance treatment with ALIMTA plus BSC (n = 359) with that of placebo plus BSC (n = 180) in patients with locally advanced (Stage IIIB) or metastatic (Stage IV) NSCLC other than predominantly squamous cell histology who did not progress after 4 cycles of first line doublet therapy of ALIMTA in combination with cisplatin. Of the 939 patients treated with ALIMTA plus cisplatin induction, 539 patients were randomised to maintenance treatment with pemetrexed or placebo. Of randomised patients, 44.9% had a complete/partial response and 51.9% had a response of stable disease to ALIMTA plus cisplatin induction. Patients randomised to maintenance treatment were required to havean ECOG performance status 0 or 1. The median time from the start of ALIMTA plus cisplatin induction therapy to the start of maintenance treatment was 2.96 months on both the pemetrexed arm and the placebo arm. Randomised patients received maintenance treatment until disease progression. Efficacy and safety were measured from the time of randomisation after completion of first line (induction) therapy. Patients received a median of 4 cycles of maintenance treatment with ALIMTA and 4 cycles of placebo. A total of 109 patients (30.4%) completed ≥ 6 cycles maintenance treatment with ALIMTA, representing at least 10 total cycles of ALIMTA. The study met its primary endpoint and showed a statistically significant improvement in PFS in the ALIMTA arm over the placebo arm (n = 472, independently reviewed population; median of 3.9 months and 2.6 months, respectively) (hazard ratio = 0.64, 95% CI = 0.51-0.81, p = 0.0002). The independent review of patient scans confirmed the findings of the investigator assessment of PFS. For randomised patients, as measured from the start of ALIMTA plus cisplatin first line induction treatment, the median investigator-assessed PFS was	תוספת בעמוד 21 המפרט נסוי קליני PARAMOUNT	**5.1PHARMACODYNAMIC PROPERTIES**

6.9 months for the ALIMTA arm and 5.59 months for the placebo arm (hazard ratio = 0.59 95% CI = 0.47-0.74). A preliminary survival analysis showed that the median survival on the ALIMTA continuation arm after induction therapy with ALIMTA/cisplatin (4 cycles) was 13.9 months versus 11.1 months for those on the placebo arm (hazard ratio = 0.78, 95% CI = 0.61-0.98, p = 0.034). At the time of this preliminary survival analysis, 48% of patients were alive on the ALIMTA arm versus 38% on the placebo arm, with a median follow-up of 11.04 months. **PARAMOUNT:Kaplan Meier plot of progression-free survival (PFS) for continuation ALIMTA maintenance versus placebo in patients with NSCLC other than predominantly squamous cell histology (independent review, measured from randomisation)** The ALIMTA maintenance safety profiles from the two studies JMEN and PARAMOUNT were similar.		

4.8 Undesirable Effects

Current Table on page 14:

System organ class	Frequency*	Event**	Pemetrexed (N = 441)		Placebo (N = 222)	
			All grades toxicity (%)	Grade 3 - 4 toxicity (%)	All grades toxicity (%)	Grade 3 - 4 toxicity (%)
~~Infections and infestations~~	~~Common~~	~~Infection~~	~~5.2~~	~~1.6~~	~~1.8~~	~~0.0~~
Blood and lymphatic system disorders	Very common	Hemoglobin	~~15.2~~	~~2.7~~	~~5.4~~	0.5
	Common	Leukocytes	~~6.1~~	1.6	~~1.4~~	~~0.5~~
		Neutrophils	~~5.9~~	~~2.9~~	~~0.0~~	0.0
Nervous system disorders	Common	Neuropathy-sensory	~~8.8~~	~~0.7~~	~~4.1~~	~~0.0~~
Gastrointestinal disorders	Very common	Nausea	~~18.8~~	~~0.9~~	~~5.4~~	~~0.5~~
		Anorexia	~~18.6~~	~~1.8~~	~~5.0~~	0.0
	Common	Vomiting	~~8.6~~	~~0.2~~	~~1.4~~	0.0
		Mucositis/ stomatitis	~~7.0~~	~~0.7~~	~~1.8~~	0.0
	~~Common~~	~~Diarrhoea~~	~~5.2~~	~~0.5~~	~~2.7~~	~~0.0~~
Hepatobiliary disorders	Common	ALT (SGPT)	~~9.5~~	~~0.2~~	~~3.6~~	0.0
		AST (SGOT)	~~8.2~~	0.0	~~3.6~~	0.0
Skin and subcutaneous tissue disorders	Very common	Rash/ desquamation	~~10.0~~	~~0.0~~	3.2	0.0
General disorders and administration site conditions	Very common	Fatigue	~~24.5~~	~~5.0~~	10.4	0.5

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	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