נובמבר 2020

רופא/ה, רוקח/ת נכבד/ה,
חברת טבע מודיעה על <u>העדכונים בעלון לרופא</u> ועל <u>עלון לצרכן חדש</u> של התכשירים:

Pemetrexed Teva 100 mg, 500mg, 1000mg
Powder for Concentrate for Solution for Infusion

פמטרקסד טבע 100 מ"ג, 500 מ"ג, 1000 מ"ג
אבקה להכנת תמיסה מרוכזת להכנת תמיסה למתן בעירוי

Pemetrexed Teva 100 mg: each vial contains 100 mg Pemetrexed
Pemetrexed Teva 500 mg: each vial contains 500 mg Pemetrexed
Pemetrexed Teva 1000 mg: each vial contains 1000 mg Pemetrexed

עדכונים בעלון לרופא ועלון לצרכן חדש

<u>התוויה כפי שאושרה בתעודת הרישום:</u>

Malignant pleural mesothelioma:
Pemetrexed Teva 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:
Pemetrexed Teva 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.

Pemetrexed Teva 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.

Pemetrexed Teva 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.

<u>עלון לרופא</u>

<u>ברצוננו להודיע שהעלון לרופא עודכן, בפירוט שלהלן כלולים העדכונים העיקריים בלבד (תוספות מסומנות באדום, החמרות מסומנות בצהוב והסרות מידע כטקסט מחוק):</u>

<u>4.2 Posology and method of administration</u>
[…]

<u>Method of administration</u>
<u>Pemetrexed Teva is for intravenous use. Pemetrexed Teva should be administered as an intravenous infusion over 10 minutes on the first day of each 21- day cycle</u>.

For precautions to be taken before handling or administering Pemetrexed Teva and for instructions on reconstitution and dilution of Pemetrexed Teva before administration, see section 6.6.
[…]

4.4 Special warnings and precautions for use
[…]

Excipients:
Sodium

Pemetrexed Teva 100 mg:

This medicinal product contains less than 1 mmol sodium (approximately 11 mg) per vial, that is to say essentially "sodium- free".

Pemetrexed Teva 500 mg:
This medicinal product contains approximately 2.3 mmol sodium (approximately 54 mg) per vial, equivalent to 2.7 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Pemetrexed Teva 1000 mg:
This medicinal product contains approximately 4.7 mmol sodium (approximately 109 mg) per vial, equivalent to 5.45% of the WHO recommended maximum daily intake of 2 g sodium for an adult.
[…]

4.8 Undesirable effects
[…]

Tabulated list of adverse reactions
The table 4 lists the adverse drug events regardless of causality associated with pemetrexed used either as a monotherapy treatment or in combination with cisplatin from the pivotal registration studies (JMCH, JMEI, JMBD, JMEN and PARAMOUNT) and from the post marketing period.

ADRs are listed by MedDRA body system organ class. The following convention has been used for classification of frequency: very common: ≥1/10; common: ≥1/100 to <1/10; uncommon: ≥1/1,000 to <1/100; rare: ≥1/10,000 to <1/1000; very rare: <1/10,000 and not known (cannot be estimated from available data).

Table 4. Frequencies of all grades adverse drug events regardless of causality from the pivotal registration studies: JMEI (pemetrexed vs docetaxel), JMDB (pemetrexed and cisplatin versus gemcitabine and cisplatin), JMCH (pemetrexed plus cisplatin versus cisplatin), JMEN and PARAMOUNT (pemetrexed plus best supportive care versus placebo plus best supportive care) and from post-marketing period.

System Organ Class (MedDRA)	Very common	Common	Uncommon	Rare	Very rare	Not known
Infections and infestations	Infection[a] Pharyngitis	Sepsis[b]			Dermo-hypodermitis	

System Organ Class (MedDRA)	Very common	Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic system disorders	Neutropenia Leukopenia Haemoglobin decreased	Febrile neutropenia Platelet count decreased	Pancytopenia	Autoimmune haemolytic anaemia		
Immune System disorders		Hyper-sensitivity		Anaphylactic shock		
Metabolism and nutrition disorders		Dehydration				
Nervous system disorders		Taste disorder Peripheral motor neuropathy Peripheral sensory neuropathy Dizziness	Cerebro-vascular accident Ischaemic stroke Haemorrhage intracranial			
Eye disorders		Conjunctivitis Dry eye Lacrimation increased Kerato-conjunctivitis sicca Eyelid oedema Ocular surface disease				
Cardiac disorders		Cardiac failure Arrhythmia	Angina Myocardial infarction Coronary artery disease Arrhythmia supra-ventricular			
Vascular disorders			Peripheral ischaemia[c]			

System Organ Class (MedDRA)	Very common	Common	Uncommon	Rare	Very rare	Not known
Respiratory, thoracic and mediastinal disorders			Pulmonary embolism Interstitial pneumonitis[bd]			
Gastrointestinal disorders	Stomatitis Anorexia Vomiting Diarrhea Nausea	Dyspepsia Constipation Abdominal pain	Rectal haemorrhage Gastro-intestinal haemorrhage Intestinal perforation Oesophagitis Colitis[e]			
Hepatobiliary disorders		Alanine amino-transferase increased Aspartate amino-transferase increased		Hepatitis		
Skin and subcutaneous tissue disorders	Rash Skin exfoliation	Hyper-pigmentation Pruritus Erythema multiforme Alopecia Urticaria		Erythema	Stevens-Johnson syndrome[b] Toxic epidermal necrolysis[b] Pemphigoid Dermatitis bullous Acquired epidermolysis bullosa Erythematous oedema[f] Pseudocellulitis Dermatitis Eczema Prurigo	
Renal and urinary disorders	Creatinine clearance decreased Blood creatinine increased[e]	Renal failure Glomerular filtration rate decreased				Nephrogenic diabetes insipidus Renal tubular necrosis

System Organ Class (MedDRA)	Very common	Common	Uncommon	Rare	Very rare	Not known
General disorders and administration site conditions	Fatigue	Pyrexia Pain Oedema Chest pain Mucosal inflammation				
Investigations		Gamma-glutamyl-transferase increased				
Injury, poisoning and procedural complications			Radiation oesophagitis Radiation pneumonitis	Recall phenomenon		

~~**Tabulated list of adverse reactions**~~

~~The table below provides the frequency and severity of undesirable effects that have been reported in > 5 % of 168 patients with mesothelioma who were randomised to receive cisplatin, and pemetrexed and 163 patients with mesothelioma randomised to receive single agent cisplatin. In both treatment arms, these chemonaive patients were fully supplemented with folic acid and vitamin B12.~~

~~Frequency estimate: Very common (≥ 1/10), common (≥ 1/100 to <1/10), uncommon (≥ 1/1000 to < 1/100), rare (≥ 1/10,000 to <1/1000), very rare (<1/10,000) and not known (cannot be estimated from available data).~~

~~Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.~~

~~System organ class~~	~~Frequency~~	~~*Event~~	~~Pemetrexed/cisplatin (N = 168)~~		~~Cisplatin (N = 163)~~	
			~~All grades toxicity (%)~~	~~Grade toxicity 4 - 3 (%)~~	~~All grades toxicity (%)~~	~~4 Grade 3 (%) toxicity~~
~~Blood and lymphatic system disorders~~	~~Very common~~	~~Neutrophils/ Granulocytes decreased~~	~~56.0~~	~~23.2~~	~~13.5~~	~~3.1~~
		~~Leukocytes decreased~~	~~53.0~~	~~14.9~~	~~16.6~~	~~0.6~~
		~~Haemoglobin decreased~~	~~26.2~~	~~4.2~~	~~10.4~~	~~0.0~~
		~~Platelets decreased~~	~~23.2~~	~~5.4~~	~~8.6~~	~~0.0~~
~~Metabolism and nutrition disorders~~	~~Common~~	~~Dehydration~~	~~6.5~~	~~4.2~~	~~0.6~~	~~0.6~~

Nervous system disorders	Very common	Neuropathy-Sensory	10.1	0.0	9.8	0.6
	Common	Taste disturbance	7.7	0.0***	6.1	0.0***
Eye disorders	Common	Conjunctivitis	5.4	0.0	0.6	0.0
Gastrointestinal disorders	Very common	Diarrhoea	16.7	3.6	8.0	0.0
		Vomiting	56.5	10.7	49.7	4.3
		Stomatitis/ Pharyngitis	23.2	3.0	6.1	0.0
		Nausea	82.1	11.9	76.7	5.5
		Anorexia	20.2	1.2	14.1	0.6
		Constipation	11.9	0.6	7.4	0.6
	Common	Dyspepsia	5.4	0.6	0.6	0.0
Skin and subcutaneous tissue disorders	Very common	Rash	16.1	0.6	4.9	0.0
		Alopecia	11.3	0.0***	5.5	0.0***
Renal and urinary disorders	Very common	Creatinine elevation	10.7	0.6	9.8	1.2
		Creatinine clearance decreased**	16.1	0.6	17.8	1.8
General disorders and administration site conditions	Very common	Fatigue	47.6	10.1	42.3	9.2

*Refer to National Cancer Institute CTC version 2 for each grade of toxicity except the term "creatinine clearance decreased".

** Which is derived from the term "renal/genitourinary other".

*** According to National Cancer Institute CTC (v2.0; NCI 1998), taste disturbance and alopecia should only be reported as Grade 1 or 2.

For the purpose of this table a cut-off of 5 % was used for inclusion of all events where the reporter considered a possible relationship to pemetrexed and cisplatin.

Clinically relevant CTC toxicities that were reported in ≥ 1 % and ≤ 5 % of the patients that were randomly assigned to receive cisplatin and pemetrexed include: renal failure, infection, pyrexia, febrile neutropenia, increased AST, ALT, and GGT, urticaria and chest pain.

Clinically relevant CTC toxicities that were reported in < 1 % of the patients that were randomly assigned to receive cisplatin and pemetrexed include arrhythmia and motor neuropathy.

The table below provides the frequency and severity of undesirable effects that have been reported in > 5 % of

265 patients randomly assigned to receive single-agent pemetrexed with folic acid and vitamin B12 supplementation and 276 patients randomly assigned to receive single-agent docetaxel. All patients were diagnosed with locally advanced or metastatic non-small cell lung cancer and received prior chemotherapy.

System organ class	Frequency	*Event	Pemetrexed N = 265		Docetaxel N = 276	
			All grades (%) toxicity	4 - Grade 3 (%) toxicity	All Grades (%) toxicity	4 - 3 Grade (%) toxicity
Blood and lymphatic system disorders	Very Common	Neutrophils/ Granulocytes decreased	10.9	5.3	45.3	40.2
		Leukocytes decreased	12.1	4.2	34.1	27.2
		Haemoglobin decreased	19.2	4.2	22.1	4.3
	Common	Platelets decreased	8.3	1.9	1.1	0.4
Gastrointestinal disorders	Very Common	Diarrhoea	12.8	0.4	24.3	2.5
		Vomiting	16.2	1.5	12.0	1.1
		Stomatitis/ Pharyngitis	14.7	1.1	17.4	1.1
		Nausea	30.9	2.6	16.7	1.8
		Anorexia	21.9	1.9	23.9	2.5
	Common	Constipation	5.7	0.0	4.0	0.0
Hepatobiliary disorders	Common	SGPT (ALT) elevation	7.9	1.9	1.4	0.0
		SGOT (AST) elevation	6.8	1.1	0.7	0.0
Skin and subcutaneous tissue disorders	Very Common	Rash/ Desquamation	14.0	0.0	6.2	0.0
	Common	Pruritus	6.8	0.4	1.8	0.0
		Alopecia	6.4	0.4**	37.7	2.2**
General disorders and administration site conditions	Very Common	Fatigue	34.0	5.3	35.9	5.4
	Common	Fever	8.3	0.0	7.6	0.0

*Refer to National Cancer Institute CTC version 2 for each grade of toxicity.

**According to National Cancer Institute CTC (v2.0; NCI 1998), alopecia should only be reported as Grade 1 or 2.

For the purpose of this table a cut-off of 5 % was used for inclusion of all events where the reporter considered a possible relationship to pemetrexed.

Clinically relevant CTC toxicities that were reported in ≥ 1 % and ≤ 5 % of the patients that were randomly assigned to pemetrexed include: infection without neutropenia, febrile neutropenia, allergic reaction/hypersensitivity, increased creatinine, motor neuropathy, sensory neuropathy, erythema multiforme, and abdominal pain.

Clinically relevant CTC toxicities that were reported in < 1 % of the patients that were randomly assigned to pemetrexed include supraventricular arrhythmias.

Clinically relevant Grade 3 and Grade 4 laboratory toxicities were similar between integrated Phase 2 results from three single-agent pemetrexed studies (N = 164) and the Phase 3 single-agent pemetrexed study described above, with the exception of neutropenia (12.8 % versus 5.3 %, respectively) and alanine aminotransferase elevation (15.2 % versus 1.9 %, respectively). These differences were likely due to differences in the patient population, since the Phase 2 studies included both chemonaive and heavily pre-treated breast cancer patients with pre-existing liver metastases and/or abnormal baseline liver function tests.
The table below provides the frequency and severity of undesirable effects considered possibly related to study drug that have been reported in > 5% of 839 patients with NSCLC who were randomised to receive cisplatin and pemetrexed and 830 patients with NSCLC who were randomised to receive cisplatin and gemcitabine. All patients received study therapy as initial treatment for locally advanced or metastatic NSCLC and patients in both treatment groups were fully supplemented with folic acid and vitamin B_{12}.

System organ class	**Frequency**	****Event**	**Pemetrexed/ Cisplatin (N = 839)**		**Gemcitabin/ Cisplatin (N = 830)**	
			All grades toxicity (%)	**4 Grade 3 (%) toxicity**	**All grades toxicity (%)**	**4 Grade 3 (%) toxicity**
Blood and lymphatic system disorders	Very common	Hemoglobin decreased	33.0*	5.6*	45.7*	9.9*
		Neutrophils/ Granulocytes decreased	29.0*	15.1*	38.4*	26.7*
		Leukocytes Decreased	17.8	4.8*	20.6	7.6*
		Platelets Decreased	10.1*	4.1*	26.6*	12.7*
Nervous system disorders	Common	Neuropathy-sensory	8.5*	0.0*	12.4*	0.6*
		Taste disturbance	8.1	0.0***	8.9	0.0***
Gastrointestinal disorders	Very common	Nausea	56.1	7.2*	53.4	3.9*
		Vomiting	39.7	6.1	35.5	6.1
		Anorexia	26.6	2.4*	24.2	0.7*
		Constipation	21.0	0.8	19.5	0.4
		Stomatitis/ Pharyngitis	13.5	0.8	12.4	0.1
		Diarrhoea without colostomy	12.4	1.3	12.8	1.6
	Common	Dyspepsia/ Heartburn	5.2	0.1	5.9	0.0
Skin and subcutaneous tissue disorders	Very common	Alopecia	11.9*	0***	21.4*	0.5***

System organ class	Frequency	**Event	Pemetrexed/ Cisplatin (N = 839)		Gemcitabin/ Cisplatin (N = 830)	
			All grades toxicity (%)	4 Grade 3 (%) toxicity	All grades toxicity (%)	4 Grade 3 (%) toxicity
	Common	Rash/ Desquamation	6.6	0.1	8.0	0.5
Renal and urinary disorders	Very common	Creatinine elevation	10.1*	0.8	6.9*	0.5
General disorders and administration site conditions	Very common	Fatigue	42.7	6.7	44.9	4.9

*p *values* <0.05 comparing pemetrexed/cisplatin to gemcitabine/cisplatin, using Fisher Exact test.

**Refer to National Cancer Institute CTC (v2.0; NCI 1998) for each Grade of Toxicity.

***According to National Cancer Institute CTC (v2.0; NCI 1998), taste disturbance and alopecia should only be reported as Grade 1 or 2.

For the purpose of this table, a cut-off of 5% was used for inclusion of all events where the reporter considered a possible relationship to pemetrexed and cisplatin.

Clinically relevant toxicity that was reported in ≥ *1%* and ≤ 5% of the patients that were randomly assigned to receive cisplatin and pemetrexed include: AST increase, ALT increase, infection, febrile neutropenia, renal failure, pyrexia, dehydration, conjunctivitis, and creatinine clearance decrease.

Clinically relevant toxicity that was reported in < 1% of the patients that were randomly assigned to receive cisplatin and pemetrexed include: GGT increase, chest pain, arrhythmia, and motor neuropathy.

Clinically relevant toxicities with respect to gender were similar to the overall population in patients receiving pemetrexed plus cisplatin.

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-based chemotherapy. Patients in both study arms were fully supplemented with folic acid and vitamin B_{12}.

System organ class	*Frequency	**Event	***Pemetrexed (N =800)		***Placebo (N =402)	
			All grades (%) toxicity	Grade 4 - 3 toxicity (%)	All grades toxicity (%)	Grade 4 - 3 toxicity (%)
Blood and lymphatic system	Very common	Hemoglobin decreased	18.0	4.5	5.2	0.5

disorders	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
		Oedema	5.6	0.0	1.5	0.0
Renal Disorders	Common	Renal disorders****	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 oxaloacetic 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.

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, diarrhoea, constipation, alopecia, pruritis/itching, fever (in the absence of neutropenia), ocular surface disease (including conjunctivitis), increased lacrimation, 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, 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=519),

and compared to patients who received > 6 cycles of pemetrexed (N=281).

Increases in adverse reactions (all grades) were observed with longer exposure; 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%, > 6 cycles: 6.4%: p=0.046). No statistically significant differences in any other individual Grade 3/4/5 adverse reactions were seen with longer exposure.

Serious cardiovascular and cerebrovascular events, including myocardial infarction, angina pectoris, cerebrovascular accident, and transient ischaemic attack have been uncommonly reported during clinical studies with pemetrexed, usually when given in combination with another cytotoxic agent. Most of the patients in whom these events have been observed had pre-existing cardiovascular risk factors.

Rare cases of hepatitis, potentially serious, have been reported during clinical studies with pemetrexed.

Pancytopenia has been uncommonly reported during clinical trials with pemetrexed.

In clinical trials, cases of colitis (including intestinal and rectal bleeding, sometimes fatal, intestinal perforation, intestinal necrosis and typhlitis) have been reported uncommonly in patients treated with pemetrexed.

In clinical trials, cases of interstitial pneumonitis with respiratory insufficiency, sometimes fatal, have been reported uncommonly in patients treated with pemetrexed.

Uncommon cases of oedema have been reported in patients treated with pemetrexed.

Oesophagitis/ radiation oesophagitis has been uncommonly reported during clinical trials with pemetrexed.

Sepsis, sometimes fatal, has been commonly reported during clinical trials with pemetrexed.

During post-marketing surveillance, the following adverse reactions have been reported in patients treated with pemetrexed:

Hyperpigmentation has been commonly reported.
Uncommon cases of acute renal failure have been reported with pemetrexed alone or in association with other chemotherapeutic agents (see section 4.4). Nephrogenic diabetes insipidus and renal tubular necrosis have been reported in post-marketing setting with an unknown frequency.
Uncommon cases of radiation pneumonitis have been reported in patients treated with radiation either prior, during or subsequent to their pemetrexed therapy (see section 4.4).
Rare cases of radiation recall have been reported in patients who have received radiotherapy previously (see section 4.4).

Uncommon cases of peripheral ischaemia leading sometimes to extremity necrosis 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, immune-mediated haemolytic anaemia has been reported in patients treated with pemetrexed.

Rare cases of anaphylactic shock have been reported.

~~Erythematous oedema mainly of the lower limbs has been reported with an unknown frequency.~~

~~Infectious and non-infectious disorders of the dermis, the hypodermis and/or the subcutaneous tissue have been reported with an unknown frequency (e.g. acute bacterial dermo-hypodermitis, pseudocellulitis, dermatitis).~~

עלון לצרכן

העלון לצרכן רצ"ב.

העלון לצרכן והעלון לרופא נשלחו לפרסום במאגר התרופות שבאתר האינטרנט של משרד הבריאות http://www.health.gov.il, וניתן לקבלו מודפס ע"י פניה לחברת טבע.