SANDOZ A Novartis Division

אפריל 2021

רופא/ה נכבד/ה,

רוקח/ת נכבד/ה,

חברת נוברטיס ישראל בע"מ מבקשת להודיעכם על עדכון עלון לרופא עבור התכשירים:

שם התכשיר	חומר פעיל וחוזקו	צורת מינון
Pemetrexed Sandoz® 100	Pemetrexed as disodium 100 mg/vial	powder for concentrate for solution for infusion
Pemetrexed Sandoz® 500	Pemetrexed as disodium 500 mg/vial	powder for concentrate for solution for infusion
Pemetrexed Sandoz® 1000	Pemetrexed as disodium 1000 mg/vial	powder for concentrate for solution for infusion

ההתוויות המאושרות לתכשיר:

Pemetrexed Sandoz 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. Pemetrexed Sandoz 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 Sandoz 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.Pemetrexed Sandoz 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.

בהודעה זו מצויינים רק הסעיפים בהם נעשו החמרות ושינויים בעלון לרופא. ההחמרות הודגשו בצהוב.

העלון לרופא נשלח לפרסום במאגר התרופות באתר משרד הבריאות:

https://data.health.gov.il/drugs/index.html#!/byDrug

כמו כן ניתן לקבלו מודפס על ידי פניה לחברת נוברטיס ישראל בע"מ.

לעדכונכם בברכה,

אבי ילצינדג
רוקח ממונה חטיבת סנדוז
נוברטיס ישראל בע"מ

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מקרא לעדכונים המסומנים:

- תוספת שאינה החמרה – כתב אדום
- טקסט שהוסר מסומן ~~באדום עם קו מחיקה~~
- תוספת החמרה – כתב אדום המסומן במרקר צהוב

4.4 Special warnings and precautions for use

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Excipients

Pemetrexed Sandoz 100 mg powder for concentrate for solution for infusion
This medicinal product contains less than 1 mmol sodium (23 mg) per vial, ~~i.e.~~that is to say essentially 'sodium-free'.

Pemetrexed Sandoz 500 mg powder for concentrate for solution for infusion
This medicinal product contains 54 mg sodium per vial~~. To be taken into consideration by patients on a controlled sodium diet.~~, equivalent to 2.7% of the WHO recommended maximum daily intake of 2 g for an adult.

Pemetrexed Sandoz 1000 mg powder for concentrate for solution for infusion
This medicinal product contains 108 mg sodium per vial, equivalent to 5.4% of the WHO recommended maximum daily intake of 2 g for an adult~~. To be taken into consideration by patients on a controlled sodium diet~~.

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4.6 Fertility, pregnancy and lactation

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Women of childbearing potential / Contraception in males and females
Women of childbearing potential must use effective contraception during treatment with pemetrexed. Pemetrexed can have genetically damaging effects. Sexually mature males are advised not to father a child during the treatment, and up to 6 months thereafter. Contraceptive measures or abstinence are recommended.

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Breast-feeding
It is ~~not~~ unknown whether pemetrexed is excreted in human milk, and adverse reactions on the breast-feeding~~suckling~~ child cannot be excluded. Breast-feeding must be discontinued during pemetrexed therapy (see section 4.3).

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4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. ~~Pemetrexed Sandoz has minor influence on the ability to drive and use machines as it~~However, it has been reported that pemetrexed may cause fatigue. Therefore, patients should be cautioned against driving or operating machines if this event occurs.

4.8 Undesirable effects

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Summary of the safety profile
The most commonly reported undesirable effects related to pemetrexed, whether used as monotherapy or in combination, are bone marrow suppression manifested as anaemia, neutropenia, ~~leucopenia~~leukopenia, thrombocytopenia; and gastrointestinal toxicities, manifested as anorexia, nausea, vomiting, diarrhoea, constipation, pharyngitis, mucositis, and stomatitis. Other undesirable effects include renal toxicities, increased aminotransferases, alopecia, fatigue, dehydration, rash, infection/sepsis and neuropathy. Rarely seen events include Stevens-Johnson syndrome and ~~Toxic~~ toxic epidermal necrolysis.

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 < 1/1,000; very rare: < 1/10,000) and not known (cannot be estimated from the available data).
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 B_{12}.

Frequency estimate: Very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), 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 3-4 toxicity (%)	All grades toxicity (%)	Grade 3-4 toxicity (%)
Blood and lymphatic system disorders	Very common	Neutrophils/Granulocytes decreased	56.0	23.2	13.5	3.1
		Leucocytes 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
Gastro-intestinal 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	Very	Creatinine elevation	10.7	0.6	9.8	1.2

urinary disorders	common	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 B_{12} 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 (%)	Grade 3-4 toxicity (%)	All grades toxicity (%)	Grade 3-4 toxicity (%)
Blood and lymphatic system disorders	Very common	Neutrophils/ Granulocytes decreased	10.9	5.3	45.3	40.2
		Leucocytes 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)		Gemcitabine/ Cisplatin (N = 830)	
			All grades toxicity (%)	Grade 3-4 toxicity (%)	All grades toxicity (%)	Grade 3-4 toxicity (%)
Blood and lymphatic system disorders	Very common	Haemoglobin decreased	33.0*	5.6*	45.7*	9.9*
		Neutrophils/ Granulocytes decreased	29.0*	15.1*	38.4*	26.7*
		Leucocytes decreased	17.8	4.8*	20.6	7.6*
		Platelets decreased	10.1*	4.1*	26.6*	12.7*
Nervous system	Common	Neuropathy sensory	8.5*	0.0*	12.4*	0.6*

disorders		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***
	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 3 - 4 toxicity (%)	All grades toxicity (%)	Grade 3 - 4 toxicity (%)
Blood and lymphatic system	Very common	Haemoglobin decreased	18.0	4.5	5.2	0.5

disorders	Common	Leucocytes 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 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 cut off 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, pruritus/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).~~

Table 4. Frequencies of all grades adverse drug events regardless of causality from the pivotal registration studies: JMEI (ALIMTA vs Docetaxel), JMDB (ALIMTA and Cisplatin versus GEMZAR and Cisplatin, JMCH (ALIMTA 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		
Blood and lymphatic system disorders	Neutropenia Leukopenia Haemoglobin decreased	Febrile neutropenia Platelet count decreased	Pancytopenia	Autoimmune haemolytic anaemia			
Immune System disorders		Hypersensitivity		Anaphylac-tic shock			
Metabolism and nutrition disorders		Dehydration					
Nervous system disorders		Taste disorder Peripheral motor neuropathy Peripheral sensory neuropathy Dizziness	Cerebrovascular accident Ischaemic stroke Haemorrhage intracranial				
Eye disorders		Conjunctivitis Dry eye Lacrimation increased Keratoconjunctivitis sicca Eyelid oedema Ocular surface disease					
Cardiac disorders		Cardiac failure Arrhythmia	Angina Myocardial infarction				

			Coronary artery disease Arrhythmia supraventricular				
Vascular disorders			Peripheral ischaemia[c]				
Respiratory, thoracic and mediastinal disorders			Pulmonary embolism Interstitial pneumonitis[bd]				
Gastrointes-tinal disorders	Stomatitis Anorexia Vomiting Diarrhoea Nausea	Dyspepsia Constipation Abdominal pain	Rectal haemorrhage Gastrointestinal haemorrhage Intestinal perforation Oesophagitis Colitis[e]				
Hepatobiliary disorders		Aalanine aminotransferase increased Aspartate aminotransferase increased		Hepatitis			
Skin and subcutaneous tissue disorders	Rash Skin exfoliation	Hyperpigmentation Pruritus Erythema multiforme Alopecia Urticaria		Erythema	Stevens-Johnson syndrome[b] Toxic epidermal necrolysis[b] Pemphigoid Dermatitis bullous Acquired epidermolysis bullosa Erythema-tous oedema[f] Pseudocellu-litis 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	
General disorders and administration	Fatigue	Pyrexia Pain					

site conditions		Oedema Chest pain Mucosal inflammation					
Investigations		Gamma-glutamyltransferase increased					
Injury, poisoning and procedural complications			Radiation oesophagitis Radiation pneumonitis	Recall phenomenon			

[a] with and without neutropenia
[b] in some cases fatal
[c] sometimes leading to extremity necrosis
[d] with respiratory insufficiency
[e] seen only in combination with cisplatin
[f] mainly of the lower limbs

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