הודעה על החמרה - מידע בטיחות בעלון לרופא

תאריך 12.12.16 :

שם תכשיר באנגלית: Docetaxel Ebewe 10 mg/1ml

מספר רישום: 146-55-33269-00

שם בעל הרישום : Pharmalogic Ltd.

טופס זה מיועד לפרוט ההחמרות בלבד !

מסומנים בצהוב אך ורק החמרות!! (טבלאות צורפו כנספחים)

	החמרות מבוקשות		
טקסט חדש	טקסט ישן		פרק בעלון
Special poulation Paediatric population The safety and efficacy of docetaxel in nasopharyngeal carcinoma in children aged 1 month to less than 18 years have not yet been established. There is no relevant use of docetaxel in the paediatric population in the indications breast cancer, non-small cell lung cancer, prostate cancer, gastric carcinoma and head and neck cancer, not including type II and III less differentiated nasopharyngeal carcinoma.	***Children and adolescents*** Docetaxel Ebewe is not recommended for use in children due to insufficient data on safety and efficacy.		**Posology and method of Administration**

Respiratory disorders: Acute respiratory distress syndrome, interstitial pneumonia/pneumonitis, interstitial lung disease, pulmonary fibrosis and respiratory failure have been reported and may be associated with fatal outcome. Cases of radiation pneumonitis have been reported in patients receiving concomitant radiotherapy. If new or worsening pulmonary symptoms develop, patients should be closely monitored, promptly investigated, and appropriately treated. Interruption of docetaxel therapy is recommended until diagnosis is available. Early use of supportive care measures may help improve the condition. The benefit of resuming docetaxel treatment must be carefully evaluated.			**Special warnings and precautions for use**
Eye disorders Cystoid macular oedema (CMO) has been reported in patients treated with docetaxel. Patients with impaired vision should undergo a prompt and complete ophthalmologic examination. In case CMO is diagnosed, docetaxel treatment should be discontinued and appropriate treatment initiated (see section 4.8).			
Others Contraceptive measures must be taken by both men and women during treatment and for men at least 6 months after cessation of therapy (see section 4.6). The concomitant use of docetaxel with strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole) should be avoided (see section 4.5).	***Others*** Contraceptive measures should be used by both men and women during and for at least three months after cessation of therapy (see section "Pregnancy & Lactation").		
Additional cautions for use in adjuvant treatment of breast cancer *Complicated neutropenia:* ***Congestive heart failure*** Patients should be monitored for symptoms of congestive heart failure during therapy and during the follow up period. In patients treated with the TAC regimen for node positive breast cancer, the risk of CHF has been shown to be higher during the first year after treatment (see sections 4.8 and 5.1).	***Congestive heart failure*** Patients should be monitored for symptoms of congestive heart failure during therapy and during the follow up period.		**Special warnings and precautions for**

Contraception in males and females An effective method of contraception should be used during treatment. **Fertility** In non clinical studies, docetaxel has genotoxic effects and may alter male fertility (see section 5.3). Therefore, men being treated with docetaxel are advised not to father a child during and up to 6 months after treatment and to seek advice on conservation of sperm prior to treatment.			**Pregnancy and lactation**

Undesirable effects

Summery of the safty profile for all indications:

1276 patients (744 and 532 in TAX 316 and GEICAM 9805 respectively) who received docetaxel in combination with doxorubicin and cyclophosphamide (clinically important treatment related adverse events are presented).

- 744 patients who received docetaxel in combination with doxorubicin and cyclophosphamide (clinically important treatment- related adverse events are presented).

Tabulated List of adverse reactions for adjuvant therapy with DOCETAXEL 75 mg/m² in combination with doxorubicin and cyclophosphamide in patients with node positive (TAX316) and node negative (geicam 9805) breast cancer-pooled data

נספח 1-מצורף לטופס החמרות

MedDRA System Organ classes	Very common adverse reactions	Common adverse reactions	Uncommon adverse reactions
Infections and infestations	Infection (G3/4: 2.4%); Neutropenic infection. (G3/4: 2.7%).		
Blood and lymphatic system disorders	Anaemia (G3/4: 3%); Neutropenia (G3/4: 59.2%); Thrombocytopenia (G3/4: 1.6%); Febrile neutropenia (G3/4: NA)		
Immune system disorders		Hypersensitivity (G3/4: 0.6%)	
Metabolism and nutrition disorders	Anorexia (G3/4: 1.5%)		
Nervous system disorders	Dysgeusia (G3/4: 0.6%); Peripheral sensory neuropathy (G3/4: 0.1%)	Peripheral motor neuropathy (G3/4: 0%);	Syncope (G3/4: 0%) Neurotoxicity (G3/4: 0%); Somnolence (G3/4: 0%)
Eye disorders	Conjunctivitis (G3/4: <0.1%)	Lacrimation increased (G3/4: <0.1%)	
Cardiac disorders		Arrhythmia (G3/4: 0.2%)	
Vascular disorders	Hot flush (G3/4: 0.5%)	Hypotension (G3/4: 0%) Phlebitis (G3/4: 0%)	Lymphoedema (G3/4: 0%)
Respiratory, thoracic and mediastinal disorders		Cough (G3/4: 0%)	
Gastrointestinal disorders	Nausea (G3/4: 5%); Stomatitis (G3/4: 8%); Vomiting (G3/4: 4.2%); Diarrhoea (G3/4: 3.4%); Constipation (G3/4: 0.5%)	Abdominal pain (G3/4: 0.4%)	
Skin and subcutaneous tissue disorders	Alopecia(persisting < 3%); Skin disorder (G3/4: 0.6%); Nail disorders (G3/4: 0.4%)		

נספח 2 מצורף לטופס החמרות

MedDRA System Organ classes	Very common adverse reactions ≥ 10% of patients	Common adverse reactions ≥ 1 to < 10% of patients	Uncommon adverse reactions ≥ 0.1 to < 1% of patients
Investigations	Weight increased or decreased (G3/4: 0.3%)		
Cardiac disorders		Arrhythmia (G3/4: 0.1%); Congestive heart failure	
Blood and lymphatic system disorders	Anemia (G3/4: 4.3%); Neutropenia (G3/4: 65.5%); Thrombocytopenia (G3/4: 2.0%); Febrile neutropenia		
Nervous system disorders	Dysgeusia (G3/4: 0.7%); Peripheral sensory neuropathy (G3/4: 0%)	Peripheral motor neuropathy (G3/4: 0%); Neurocortical (G3/4: 0.3%); Neurocerebellar (G3/4: 0.1%)	Syncope (G3/4: 0%)
Eye disorders		Lacrimation disorder (G3/4: 0.1%); Conjunctivitis (G3/4: 0.3%)	
Respiratory, thoracic and mediastinal disorders		Cough (G3/4: 0%)	
Gastrointestinal disorders	Nausea (G3/4: 5.1%); Stomatitis (G3/4: 7.1%); Vomiting (G3/4: 4.3%); Diarrhea (G3/4: 3.2%); Constipation (G3/4: 0.4%)	Abdominal pain (G3/4: 0.5%)	Colitis/enteritis/large intestine perforation
Skin and subcutaneous tissue disorders	Alopecia; Skin toxicity (G3/4: 0.7%); Nail disorders (G3/4: 0.4%)		
Musculoskeletal and connective tissue disorders	Myalgia (G3/4: 0.8%); Arthralgia (G3/4: 0.4%)		
Metabolism and nutrition disorders	Anorexia (G3/4: 2.2%)		
Infections and infestations	Infection (G3/4: 3.2%), Neutropenic infection. There were no septic deaths.		
Vascular disorders	Vasodilatation (G3/4: 0.9%)	Hypotension (G3/4: 0%)	Phlebitis (G3/4: 0%); Lymphoedema (G3/4: 0%)
General disorders and administration site conditions	Asthenia (G3/4: 11%); Fever (G3/4: 1.2%), Edema peripheral (G3/4: 0.4%)		
Immune system disorders	Hypersensitivity (G3/4: 1.1%)		
Reproductive system and breast disorders	Amenorrhea		

Cardiac disorders

Congestive Heart Failure (CHF) (2.3% at 70 months median follow-up) has also

5.1 Pharmacodynamic properties

Patients with operable node-positive breast cancer (TAX 316)

Two interim analyses and one final analysis were performed. The first interim analysis was planned 3 years after the date when half of study enrollment was done. The second interim analysis was done after 400 DFS events had been recorded overall, which led to a median follow-up of 55 months. The final analysis was performed when all patients had reached their 10-year follow-up visit (unless they had a DFS event or were lost to followup before). Disease-free survival (DFS) was the primary efficacy endpoint and Overall survival (OS) was the secondary efficacy endpoint

A final analysis was performed with an actual median follow up of 96 months. Significantly longer disease-free survival for the TAC arm compared to the FAC arm was demonstrated. Incidence of relapses at 10 years was reduced in patients receiving TAC compared to those who received FAC (39% versus 45%, respectively) i.e. an absolute risk reduction by 6% (p = 0.0043). Overall survival at 10 years was also significantly increased with TAC compared to FAC (76% versus 69%, respectively) i.e. an absolute reduction of the risk of death by 7% (p = 0.002). As the benefit observed in patients with 4+ nodes was not statistically significant on DFS and OS, the positive benefit/risk ratio for TAC in patients with 4+ nodes was not fully demonstrated at the final analysis.
Overall, the study results demonstrate a positive benefit risk ratio for TAC compared to FAC.

TAC-treated patient subsets according to prospectively defined major prognostic factors were analyzed:

נספח 5 מצורף לטופס החמרות

Patient subset	Number of patients	Disease Free Survival: Hazard ratio*	Disease Free Survival: 95% CI	Disease Free Survival: p =	Overall Survival: Hazard ratio*	Overall Survival: 95% CI	Overall Survival: p =
No of positive nodes							
Overall	745	0.80	0.68-0.93	0.0043	0.74	0.61-0.90	0.0020
1-3	467	0.72	0.58-091	0.0047	0.62	0.46-0.82	0.0008
4+	278	0.87	0.70-1.09	0.2290	0.87	0.67-1.12	0.2746

*a hazard ratio of less than 1 indicates that TAC is associated with a longer disease-free survival and overall survival compared to FAC

Patients with operable node-negative breast

5.1 Pharmacodynamic properties

Patients with operable node-positive breast cancer (TAX 316)

An interim analysis was performed with a median follow up of 55 months. Significantly longer disease-free survival for the TAC arm compared to the FAC arm was demonstrated. Incidence of relapses at 5 years was reduced in patients receiving TAC compared to those who received FAC (25% versus 32%, respectively) i.e. an absolute risk reduction by 7% (p = 0.001). Overall survival at 5 years was also significantly increased with TAC compared to FAC (87% versus 81%, respectively) i.e. an absolute reduction of the risk of death by 6% (p = 0.008). TAC-treated patient subsets according to prospectively defined major prognostic factors were analyzed:

נספח 4 מצורף לטופס החמרות

Patient subset	Number of patients	Disease Free Survival: Hazard ratio*	Disease Free Survival: 95% CI	Disease Free Survival: p =	Overall Survival: Hazard ratio*	Overall Survival: 95% CI	Overall Survival: p =
No of positive nodes							
Overall	745	0.72	0.59-0.88	0.001	0.70	0.53-0.91	0.008
1-3	467	0.61	0.46-0.82	0.0009	0.45	0.29-0.70	0.0002
4+	278	0.83	0.63-1.08	0.17	0.94	0.66-1.33	0.72

*a hazard ratio of less than 1 indicates that TAC is associated with a longer disease-free survival and overall survival compared to FAC

The beneficial effect of TAC was not proven in patients with 4 and more positive nodes (37% of the population) at the interim analysis stage. The effect appears to be less pronounced than in patients with 1-3 positive nodes. The benefit/risk ratio was not defined fully in patients with 4 and more positive nodes at this analysis stage.

PHARMACOLOGICAL PROPERTIES

PHARMACOLOGICAL PROPERTIES

cancer eligible to receive chemotherapy (GEICAM 9805) Data from a multicenter open label randomized trial support the use of docetaxel for the adjuvant treatment of patients with operable node-negative breast cancer eligible to receive chemotherapy. 1060 patients were randomized to receive either docetaxel 75 mg/m2 administered 1-hour after doxorubicin 50 mg/m2 and cyclophosphamide 500 mg/m2 (539 patients in TAC arm), or doxorubicin 50 mg/m2 followed by fluorouracil 500 mg/m2and cyclosphosphamide 500 mg/m2 (521 patients in FAC arm), as adjuvant treatment of operable node-negative breast cancer patients with high risk of relapse according to 1998 St. Gallen criteria (tumour size >2 cm and/or negative ER and PR and/or high histological/nuclear grade (grade 2 to 3) and /or age <35 years).). Both regimens were administered once every 3 weeks for 6 cycles. Docetaxel was administered as a 1-hour infusion, all other drugs were given intravenously on day 1 every three weeks. Primary prophylactic G-CSF was made mandatory in TAC arm after 230 patients were randomized. The incidence of Grade 4 neutropenia, febrile neutropenia and neutropenic infection was decreased in patients who received primary G-CSF prophylaxis (see section 4.8). In both arms, after the last cycle of chemotherapy, patients with ER+ and/or PgR+ tumours received tamoxifen 20 mg once a day for up to 5 years. Adjuvant radiation therapy was administered according to guidelines in place at participating institutions and was given to 57.3% of patients who received TAC and 51.2% of patients who received FAC. One primary analysis and one updated analysis were performed. The primary analysis was done when all patients had a follow-up of greater than 5 years (median follow-up time of 77 months). The updated analysis was performed when all patients had reached their 10-year (median follow up time of 10 years and 5 months) follow-up visit (unless they had a DFS event or were lost to follow-up previously). Disease-free survival (DFS) was the primary efficacy endpoint and Overall survival (OS) was the secondary efficacy endpoint. At the median follow-up time of 77 months, significantly longer disease-free survival for the TAC arm compared to the FAC arm was demonstrated. TAC-treated patients had a 32% reduction in the risk of relapse compared to those treated with FAC (hazard ratio = 0.68, 95% CI (0.49-0.93), p = 0.01). At the			**PHARMACOLOGICAL PROPERTIES**

median follow up time of 10 years and 5 months, TAC-treated patients had a 16,5% reduction in the risk of relapse compared to those treated with FAC (hazard ratio = 0.84, 95% CI (0.65-1.08), p=0.1646). DFS data were not statistically significant but were still associated with a positive trend in favour of TAC.

TAC-treated patients having a 24% reduction in the risk of death compared to FAC (hazard ratio = 0.76, 95% CI (0.46-1.26, p = 0.29). However, the distribution of OS was not significantly different between the 2 groups.
At the median follow up time of 10 years and 5 months, TAC-treated patients had a 9% reduction in the risk of death compared to FAC-treated patients (hazard ratio = 0.91, 95% CI (0.63-1.32)).
The survival rate was 93.7% in the TAC arm and 91.4 % in the FAC arm, at the 8-year follow-up timepoint, and 91.3 % in the TAC arm and 89 % in the FAC arm, at the 10-year follow-up timepoint.
The positive benefit risk ratio for TAC compared to FAC remained unchanged.

TAC-treated patient subsets according to prospectively defined major prognostic factors were analyzed in the primary analysis (at the median follow-up time of 77 months) (see table below):
Subset Analyses-Adjuvant Therapy in Patients with Node-negative Breast Cancer Study (Intent-toTreat Analysis)

נספח 6 מצורף לטופס החמרות

Patient subset	Number of patients in TAC group	Disease Free Survival	
		Hazard ratio*	95% CI
Overall	539	0.68	0.49-0.93
Age category 1 <50 years ≥50 years	 260 279	 0.67 0.67	 0.43-1.05 0.43-1.05
Age category 2 <35 years ≥35 years	 42 497	 0.31 0.73	 0.11-0.89 0.52-1.01
Hormonal receptor status Negative Positive	 195 344	 0.7 0.62	 0.45-1.1 0.4-0.97
Tumour size ≤2 cm >2 cm	 285 254	 0.69 0.68	 0.43-1.1 0.45-1.04
Histological grade Grade1 (includes grade not assessed) Grade 2 Grade 3	 64 216 259	 0.79 0.77 0.59	 0.24-2.6 0.46-1.3 0.39-0.9
Menopausal status Pre-Menopausal Post-Menopausal	 285 254	 0.64 0.72	 0.40-1 0.47-1.12

*a hazard ratio (TAC/FAC) of less than 1 indicates that TAC is associated with a longer disease free survival compared to FAC.

PHARMACOLOGICAL PROPERTIES

Exploratory subgroup analyses for disease-free survival for patients who meet the 2009 St. Gallen chemotherapy criteria – (ITT population) were performed and presented here below

נספח 7 מצורף לטופס החמרות

	TAC	FAC	Hazard ratio (TAC/FAC)	
Subgroups	(n=539)	(n=521)	(95% CI)	**p-value**
Meeting relative indication for chemotherapy a				
No	18/214 (8.4%)	26/227 (11.5%)	0.796 (0.434 - 1.459)	0.4593
Yes	48/325 (14.8%)	69/294 (23.5%)	0.606 (0.42 - 0.877)	0.0072

TAC = docetaxel, doxorubicin and cyclophosphamide
FAC = 5-fluorouracil, doxorubicin and cyclophospamide
CI = confidence interval; ER = estrogen receptor
PR = progesterone receptor · ER/PR-negative or Grade 3 or tumor size 5

The estimated hazard ratio was using Cox proportional hazard model with treatment group

PHARMACOLOGICAL PROPERTIES

as the fact Efficacy of docetaxel in the induction treatment of patients with locally advanced SCCHN (Intent-to-Treat Analysis) **Paediatric population** The European Medicines Agency has waived the obligation to submit the results of studies with docetaxel in all subsets of the paediatric population in breast cancer, non-small cell lung cancer, prostated cancer, gastric carcinoma and head and neck cancer, not including type II and III less differentiated nasopharyngeal carcinoma (see section 4.2 for information on paediatric use)			

נספח 1-מצורף לטופס החמרות

Tabulated List of adverse reactions for adjuvant therapy with DOCETAXEL 75 mg/m² in combination with doxorubicin and cyclophosphamide in patients with node positive (TAX316) and node negative (geicam 9805) breast cancer-pooled data

MedDRA System Organ classes	Very common adverse reactions	Common adverse reactions	Uncommon adverse reactions
Infections and infestations	Infection (G3/4: 2.4%); Neutropenic infection. (G3/4: 2.7%).		
Blood and lymphatic system disorders	Anaemia (G3/4: 3%); Neutropenia (G3/4: 59.2%); Thrombocytopenia (G3/4: 1.6%); Febrile neutropenia (G3/4: NA)		
Immune system disorders		Hypersensitivity (G3/4: 0.6%)	
Metabolism and nutrition disorders	Anorexia (G3/4: 1.5%)		

Nervous system disorders	Dysgeusia (G3/4: 0.6%); Peripheral sensory neuropathy (G3/4: 0.1%)	Peripheral motor neuropathy (G3/4: 0%);	Syncope (G3/4: 0%) Neurotoxicity (G3/4: 0%); Somnolence (G3/4: 0%)
Eye disorders	Conjunctivitis (G3/4: <0.1%)	Lacrimation increased (G3/4: <0.1%)	
Cardiac disorders		Arrhythmia (G3/4: 0.2%)	
Vascular disorders	Hot flush (G3/4: 0.5%)	Hypotension (G3/4: 0%) Phlebitis (G3/4: 0%)	Lymphoedema (G3/4: 0%)
Respiratory, thoracic and mediastinal disorders		Cough (G3/4: 0%)	
Gastrointestinal disorders	Nausea (G3/4: 5%); Stomatitis (G3/4: 6%); Vomiting (G3/4: 4.2%); Diarrhoea (G3/4: 3.4%); Constipation (G3/4: 0.5%)	Abdominal pain (G3/4: 0.4%)	
Skin and subcutaneous tissue disorders	Alopecia(persisting < 3%); Skin disorder (G3/4: 0.6%); Nail disorders (G3/4: 0.4%)		
Musculoskeletal and connective tissue disorders	Myalgia (G3/4: 0.7%); Arthralgia (G3/4: 0.2%)		
Reproductive system and breast disorders	Amenorrhoea (G3/4: NA)		
General disorders and administration site conditions	Asthenia (G3/4: 10%); Pyrexia (G3/4: NA); Oedema peripheral (G3/4: 0.2%)		

Investigations		Weight increased (G3/4: 0%); Weight decreased (G3/4: 0.2%)	

נספח 2 מצורף לטופס החמרות

DOCETAXEL 75 mg/m² in combination with doxorubicin and cyclophosphamide

MedDRA System Organ classes	**Very common adverse reactions ≥ 10% of patients**	**Common adverse reactions ≥ 1 to < 10% of patients**	**Uncommon adverse reactio 0.1 to < 1% of patients**
Investigations	Weight increased or decreased (G3/4: 0.3%)		
Cardiac disorders		Arrhythmia (G3/4: 0.1%); Congestive heart failure	
Blood and lymphatic system disorders	Anemia (G3/4: 4.3%); Neutropenia (G3/4: 65.5%); Thrombocytopenia (G3/4: 2.0%); Febrile neutropenia		
Nervous system disorders	Dysgeusia (G3/4: 0.7%); Peripheral sensory neuropathy (G3/4: 0%)	Peripheral motor neuropathy (G3/4: 0%); Neurocortical (G3/4: 0.3%); Neurocerebellar (G3/4: 0.1%)	Syncope (G3/4: 0%)
Eye disorders		Lacrimation disorder (G3/4: 0.1%); Conjunctivitis (G3/4: 0.3%)	
Respiratory, thoracic and		Cough (G3/4: 0%)	

mediastinal disorders			
Gastrointestinal disorders	Nausea (G3/4: 5.1%); Stomatitis (G3/4: 7.1%); Vomiting (G3/4: 4.3%); Diarrhea (G3/4: 3.2%); Constipation (G3/4: 0.4%)	Abdominal pain (G3/4: 0.5%)	Colitis/enteritis/large intestine perforation
Skin and subcutaneous tissue disorders	Alopecia; Skin toxicity (G3/4: 0.7%); Nail disorders (G3/4: 0.4%)		
Musculoskeletal and connective tissue disorders	Myalgia (G3/4: 0.8%); Arthralgia (G3/4: 0.4%)		
Metabolism and nutrition disorders	Anorexia (G3/4: 2.2%)		
Infections and infestations	Infection (G3/4: 3.2%); Neutropenic infection. There were no septic deaths.		
Vascular disorders	Vasodilatation (G3/4: 0.9%)	Hypotension (G3/4: 0%)	Phlebitis (G3/4: 0%); Lymphoedema (G3/4: 0%)
General disorders and administration site conditions	Asthenia (G3/4: 11%); Fever (G3/4: 1.2%); Edema peripheral (G3/4: 0.4%)		
Immune system disorders	Hypersensitivity (G3/4: 1.1%)		
Reproductive system and breast disorders	Amenorrhea		

נספח 3 מצורף לטופס החמרות

Neutropenic complications in patients receiving TAC with or without primary G-CSF prophylaxis (GEICAM 9805)

	Without primary G-CSF prophylaxis (n = 111) n (%)	With primary G-CSF prophylaxis (n = 421) n (%)
Neutropenia (Grade 4)		
Febrile neutropenia	104 (93.7) 28 (25.2)	135 (32.1) 23 (5.5)
Neutropenic infection		21 (5.0)

	14 (12.6)	
Neutropenic infection (Grade 3-4)	2 (1.8)	5 (1.2)

נספח 4 מצורף לטופס החמרות

		Disease Free Survival			Overall Survival		
Patient subset	**Number of patients**	**Hazard ratio***	**95% CI**	**p =**	**Hazard ratio***	**95% CI**	**p =**
No of positive nodes							
Overall	745	0.72	0.59-0.88	0.001	0.70	0.53-0.91	0.008
1-3	467	0.61	0.46-0.82	0.0009	0.45	0.29-0.70	0.0002
4+	278	0.83	0.63-1.08	0.17	0.94	0.66-1.33	0.72

נספח 5 מצורף לטופס החמרות

		Disease Free Survival			Overall Survival		
Patient subset	Number of patients	Hazard ratio*	95% CI	p =	Hazard ratio*	95% CI	p =
No of positive nodes							
Overall	745	0.80	0.68-0.93	0.0043	0.74	0.61-0.90	0.0020
1-3	467	0.72	0.58-091	0.0047	0.62	0.46-0.82	0.0008
4+	278	0.87	0.70-1.09	0.2290	0.87	0.67-1.12	0.2746

*a hazard ratio of less than 1 indicates that TAC is associated with a longer disease-free survival and overall survival compared to FAC

נספח 6 מצורף לטופס החמרות

Subset Analyses-Adjuvant Therapy in Patients with Node-negative Breast Cancer Study (Intent-toTreat Analysis)

Patient subset	Number of patients in TAC group	Disease Free Survival	
		Hazard ratio*	95% CI
Overall	539	0.68	0.49-0.93
Age category 1			
<50 years	260	0.67	0.43-1.05
≥50 years	279	0.67	0.43-1.05
Age category 2			
<35 years	42	0.31	0.11-0.89
≥35 years	497	0.73	0.52-1.01

Hormonal receptor status Negative Positive	 195 344	 0.7 0.62	 0.45-1.1 0.4- 0.97
Tumour size ≤2 cm >2 cm	 285 254	 0.69 0.68	 0.43-1.1 0.45-1.04
Histological grade Grade1 (includes grade not assessed) Grade 2 Grade 3	 64 216 259	 0.79 0.77 0.59	 0.24-2.6 0.46-1.3 0.39-0.9
Menopausal status Pre-Menopausal Post-Menopausal	 285 254	 0.64 0.72	 0.40-1 0.47-1.12

*a hazard ratio (TAC/FAC) of less than 1 indicates that TAC is associated with a longer disease free survival compared to FAC.

נספח 7 מצורף לטופס החמרות

Exploratory subgroup analyses for disease-free survival for patients who meet the 2009 St. Gallen chemotherapy criteria – (ITT population) were performed and presented here below

	TAC	**FAC**	**Hazard ratio (TAC/FAC)**	
Subgroups	(n=539)	(n=521)	(95% CI)	**p-value**
Meeting relative indication for chemotherapy a				

No	18/214 (8.4%)	26/227 (11.5%)	0.796 (0.434 - 1.459)	0.4593
Yes	48/325 (14.8%)	69/294 (23.5%)	0.606 (0.42 - 0.877)	0.0072

TAC = docetaxel, doxorubicin and cyclophosphamide
FAC = 5-fluorouracil, doxorubicin and cyclophospamide
CI = confidence interval; ER = estrogen receptor
PR = progesterone receptor · ER/PR-negative or
Grade 3 or tumor size >5 cm