

GENERAL DISORDERS			
General Disorders NEC			
Fatigue/Malaise/Asthenia	4	7	6
RESPIR/THORACIC/MEDIAST			
Respiratory Disorders NEC			
Rhinorrhea	0	1	0
Dyspnea	2	1	1
Upper Respiratory Tract Disorder	7	5	4
SKIN/SUBCUTANEOUS TISSUE			
Epidermal and Dermal Conditions			
Rash	1	3	2
Pruritis	0	1	1
METABOLISM & NUTRITION			
Appetite/General Nutrition Disorders			
Increased appetite	4	3	2
Decreased appetite/Anorexia	1	2	1

*Includes PTs Abdominal (pain, pain upper, pain lower, discomfort, tenderness, distension) and Stomach discomfort
 **Includes PTs Insomnia/Initial Insomnia/Middle insomnia/Early morning awakening
 Initial dose titration was beneficial in reducing the occurrence of nausea. An additional 12 weeks of CHAMPIX 1.0 mg BID was well-tolerated in patients who had completed 12 weeks of treatment and had stopped smoking. Adverse events resulted in treatment discontinuation in 1.7% of patients who received CHAMPIX compared with 1.3% of placebo patients. **Safety Study, One Year Double-blind Drug Treatment:** The overall pattern and the frequency of adverse events during a 52-week trial with CHAMPIX 1.0 mg BID (n=251 subjects randomized to CHAMPIX arm, and n=126 to placebo arm) were similar to those described in Table 2, except for the following events which were seen to be increased relative to placebo, as compared to the profile for 12 week drug exposure: nausea (40% vs 8% placebo); and the pooled terms of: abdominal pain (17% vs 3% placebo), and increased blood pressure (11% vs 6% placebo). Few of these events were recorded as severe. **Less Common Clinical Trial Adverse Drug Reactions:** In the paragraphs that follow, the frequency of less commonly reported adverse events from clinical trials is presented. The variability associated with adverse event reporting and the terminology used to describe adverse events limit the value of the quantitative frequency estimates provided. It is important to emphasize that although the events reported occurred during treatment with CHAMPIX, they were not necessarily caused by it. All reported events are included except those already listed in Table 2, those too general to be informative, and those not reasonably associated with the use of the drug. In some cases, separate event terms have been consolidated to facilitate meaningful presentation. Events are further classified within system organ class categories and enumerated in order of decreasing frequency using the following definitions: frequent (occurring in at least 1/100 patients); infrequent (occurring in <1/100 to 1/1000 patients) and rare (occurring in fewer than 1/1000 patients). **Blood and Lymphatic System Disorders: Infrequent:** Anemia, Lymphadenopathy. **Rare:** Leukocytosis, Thrombocytopenia, Splenomegaly. **Cardiac Disorders: Infrequent:** Angina pectoris, Arrhythmia, Atrial fibrillation, Bradycardia, Ventricular extrasystoles, Myocardial infarction, Palpitations, Tachycardia. **Rare:** Cardiac flutter, Coronary artery disease, Cor pulmonale, Acute coronary syndrome. **Ear and Labyrinth Disorders: Infrequent:** Tinnitus, Vertigo. **Rare:** Deafness, Meniere's disease. **Endocrine Disorders: Infrequent:** Thyroid gland disorders. **Eye Disorders: Infrequent:** Conjunctivitis, Dry eye, Eye irritation, Scotoma, Scleral discoloration, Vision blurred, Visual disturbance, Eye pain, Mydriasis, Myopia, Lacrimation increased, Photophobia. **Rare:** Acquired night blindness, Blindness transient, Cataract subcapsular, Ocular vascular disorder, Vitreous floaters. **Gastrointestinal Disorders: Frequent:** Diarrhea, Gingivitis. **Infrequent:** Change of bowel habit, Abnormal feces, Aphthous stomatitis, Gingival pain, Tongue coated, Dysphagia, Enterocolitis, Eructation, Gastritis, Gastrointestinal hemorrhage, Hematemesis, Hematochezia, Mouth ulceration, Esophagitis. **Rare:** Gastric ulcer, Intestinal obstruction, Pancreatitis acute. **General Disorders and Administration Site Conditions: Frequent:** Chest pain, Influenza like illness, Edema, Thirst. **Infrequent:** Chest discomfort, Chills, Circadian rhythm sleep disorder, feeling cold, Cyst, Pyrexia. **Hepatobiliary Disorders: Infrequent:** Gall bladder disorder. **Immune System Disorders: Infrequent:** Hypersensitivity. **Rare:** Drug hypersensitivity. **Infections and Infestations: Infrequent:** Bronchitis, Nasopharyngitis, Sinusitis, Fungal infection, Viral infection. **Investigations: Frequent:** Liver function test abnormal, Weight increased. **Infrequent:** Blood pressure increased, Electrocardiogram abnormal, Electrocardiogram T wave amplitude decreased, Electrocardiogram ST segment depression, Heart rate increased, Platelet count decreased, Semen abnormal, C-reactive protein increased, Blood calcium decreased, Muscle enzyme increased, Urine analysis abnormal. **Metabolism and Nutrition Disorders: Infrequent:** Polydipsia, Diabetes mellitus, Hyperlipidemia, Hypokalemia. **Rare:** Hyperkalemia, Hypoglycemia. **Musculoskeletal and Connective Tissue Disorders: Frequent:** Arthralgia, Back pain, Muscle cramp, Musculoskeletal pain, Myalgia. **Infrequent:** Arthritis, Chest wall pain, Costochondritis, Joint stiffness, Muscle spasms, Osteoporosis. **Rare:** Myositis. **Nervous System Disorders: Frequent:** Disturbance in attention, Dizziness, Sensory disturbance, Somnolence. **Infrequent:** Amnesia, Coordination abnormal, Dysarthria, Dysphoria, Hypertonia, Hypoesthesia, Hypoguesia, Libido increased, Libido decreased, Migraine, Parosmia, Psychomotor hyperactivity, Restlessness, Restless legs syndrome, Syncope, Tremor. **Rare:** Balance disorder, Cerebrovascular accident, Convulsion, Facial palsy, Mental impairment, Multiple sclerosis, Nystagmus, Psychomotor skills impaired, Transient ischemic attack, Visual field defect. **Psychiatric Disorders: Frequent:** Anxiety, Depression, Emotional disorder, Irritability, Restlessness. **Infrequent:** Aggression, Agitation, Disorientation, Dissociation, Mood swings, Panic reaction, Bradypnea, Thinking abnormal. **Rare:** Euphoric mood, Hallucination, Psychotic disorder, Suicidal ideation, Suicide. **Renal and Urinary Disorders: Frequent:** Polyuria. **Infrequent:** Glycosuria, Nephrolithiasis, Nocturia, Urine abnormality, Urinary syndrome. **Rare:** Renal failure acute, Urinary retention. **Reproductive System and Breast Disorders: Frequent:** Menstrual disorder. **Infrequent:** Erectile dysfunction, Menorrhagia, Vaginal discharge, Sexual dysfunction. **Respiratory, Thoracic and Mediastinal Disorders: Frequent:** Epistaxis, Respiratory disorders. **Infrequent:** Asthma, Cough, Hoarseness, Pharyngolaryngeal pain, Throat irritation, Respiratory tract congestion, Sinus congestion, Post nasal drip, Rhinorrhea, Snoring. **Rare:** Pleurisy, Pulmonary embolism. **Skin and Subcutaneous Tissue Disorders: Frequent:** Hyperhidrosis, Pruritus, Rash generalized. **Infrequent:** Acne, Dermatitis, Dry skin, Eczema, Erythema, Psoriasis, Night sweats, Urticaria. **Rare:** Photosensitivity reaction. **Vascular Disorders: Frequent:** Hot flush, Hypertension. **Infrequent:** Hypotension, Peripheral ischemia, Thrombosis. **OVERDOSAGE: Symptoms:** Consistent with its pharmacological profile, CHAMPIX resulted in increased incidences of nausea and vomiting when given at doses greater than the recommended dose of 1.0 mg BID. **Treatment:** Varfeniline has been shown to be dialyzed in patients with end-stage renal disease (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions: Renal Impairment), however, there is no experience with dialysis following overdose. **DOSE AND ADMINISTRATION: Dosing Considerations:** Smoking-cessation therapies are more likely to succeed for patients who are motivated to stop smoking and who are provided additional counselling and/or support services. Physicians should review the patient's overall smoking-cessation plan that includes treatment with CHAMPIX. There is little clinical experience with doses above the maximum recommended dose of 1.0 mg BID. **Patients with Impaired Renal Function:** For patients with severe renal impairment, daily dosage should be adjusted accordingly (see Recommended Dose and Dosage Adjustment: Special Populations, Patients with Impaired Renal Function, below). **Recommended Dose and Dosage Adjustment: Adults:** To optimize the success of the therapy, patients should be titrated up to the maximum recommended dose of 1.0 mg twice daily, using the following 1-week titration schedule: Days 1 - 3: 0.5 mg once daily; Days 4 - 7: 0.5 mg twice daily; Days 8 - End of treatment: 1.0 mg twice daily. Patients who cannot tolerate adverse effects of CHAMPIX may have the dose lowered temporarily or permanently. The patient should set a date to stop smoking. CHAMPIX dosing should start 1-2 weeks before this date. Patients should be treated with CHAMPIX for 12 weeks. For patients who have successfully stopped smoking at the end of 12 weeks, an additional course of 12 weeks treatment with CHAMPIX may be considered. No data are available on the efficacy of an additional 12 week course of treatment for patients who do not succeed in stopping smoking or who relapse after treatment. Dose tapering may be considered. Regardless of whether the treatment course is 12 or 24 weeks, risk of smoking-cessation relapse is elevated in the period immediately following the end of drug treatment (see CLINICAL TRIALS in the Product Monograph). In addition, dose tapering may help minimize discontinuation symptoms (eg. increase in irritability, urge to smoke, depression, and/or insomnia), observed in up to 3% of patients at the end of treatment. **Special Populations: Patients with Impaired Renal Function:** No dosage adjustment is necessary for patients with mild (estimated creatinine clearance >30 mL/min and <50 mL/min) to moderate (estimated creatinine clearance >30 mL/min and <50 mL/min) renal impairment. For patients who experience intolerable adverse events, dosing may be reduced. For patients with severe renal impairment, the recommended dose of CHAMPIX is 0.5 mg twice daily. Dosing should begin at 0.5 mg once daily for the first 3 days then increased to 0.5 mg twice daily. Based on insufficient clinical experience with CHAMPIX in patients with end-stage renal disease, treatment is not recommended in this patient population (see also WARNINGS AND PRECAUTIONS, Special Populations: Renal Impairment). **Patients with Hepatic Impairment:** No dosage adjustment is necessary for patients with hepatic impairment. **Psychiatric Patients, Patients with Epilepsy, Patients undergoing Chemotherapy, Patients with GI disturbances such as irritable bowel, and in general, patients with heart disease or COPD:** The use of CHAMPIX has not been studied in these patient populations (see WARNINGS AND PRECAUTIONS, Special Populations). **Dosing in Elderly Patients:** No dosage adjustment is necessary for elderly patients with normal renal function. However, varfeniline is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see WARNINGS AND PRECAUTIONS, Special Populations: Geriatrics). **Use in Children:** Safety and effectiveness of CHAMPIX in pediatric patients have not been established; therefore, CHAMPIX is not recommended for use in patients under 18 years of age. **Administration:** CHAMPIX is given orally with or without food (see ACTION AND CLINICAL PHARMACOLOGY, DOSAGE FORMS, COMPOSITION AND PACKAGING: CHAMPIX is supplied for oral administration in two strengths: 0.5 mg: capsular biconvex, white to off-white, film-coated tablet debossed with "Pfizer" on one side and "CHX 0.5" on the other side. Each tablet contains 0.5 mg of varfeniline (as tartrate). Supplied in high-density polyethylene (HDPE) bottles of 56 tablets and in blister strips of 11 tablets. 1.0 mg: capsular biconvex, light blue film-coated tablet debossed with "Pfizer" on one side and "CHX 1.0" on the other side. Each tablet contains 1.0 mg of varfeniline (as tartrate). Supplied in blister strips of 14 tablets. Initial dosing pack: Includes 0.5 mg tablets in blister strips of 11 tablets and 1.0 mg tablets in blister strips of 14 tablets. Nonmedicinal ingredients are microcrystalline cellulose, anhydrous dibasic calcium phosphate, croscarmellose sodium, colloidal silicon dioxide and magnesium stearate. The film-coating contains hypromellose, titanium dioxide, polyethylene glycol and triacetin. The 1.0 mg tablet also contains FD&C Blue #2/Indigo Carmine Aluminum Lake as a colouring agent. **STORAGE AND STABILITY:** Store at room temperature (15-30°C). **References:** 1. CHAMPIX Product Monograph, Pfizer Canada Inc., January 2007. 2. Gonzales D et al. Varfeniline, an $\alpha 4\beta 2$ nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking-cessation: A randomized controlled trial. JAMA 2006;296:47-55. 3. Jorenby DE et al. Efficacy of varfeniline, an $\alpha 4\beta 2$ nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking-cessation: A randomized controlled trial. JAMA 2006;296:56-63.

Penz ED, Joffres MR, Campbell NR. Reducing dietary sodium and decreases in cardiovascular disease in Canada. *Can J Cardiol* 2008;24(6):497-501.

The authors report two errors in the above article. In estimating the effects of reducing blood pressure on cardiovascular events, RR were used for myocardial infarction, cerebrovascular and congestive heart failure events associated with a specific reduction in blood pressure from a meta-analysis of antihypertensive trials. The RR for myocardial infarction, cerebrovascular and congestive heart failure events associated with diuretic therapy were 0.79, 0.71 and 0.51, respectively; however, RR of 0.87, 0.68 and 0.60, respectively, were used in the above-named article. In addition, the number of congestive heart failure hospitalizations and deaths in Canada in 2002 was 56,186, rather than the reported 9488. Table 1 highlights the revised decrease in cardiovascular events associated with different reductions in sodium intake and hypertension control rates. Table 2 highlights the proportion of all cardiovascular events prevented using the new RR and congestive heart failure events. The authors regret the errors.

TABLE 1
Estimated reduction in cardiovascular events associated with different reductions in dietary sodium and alternate treatment and control rates of hypertension

	MI		Stroke		CHF		Total	
	Original	Revised*	Original	Revised*	Original	Revised†	Original	Revised†
2400 mg	5447	8801	8987	8145	2341	16,984	16,775	33,930
13% control	5134	8295	8419	7630	2187	15,866	15,740	31,791
66% control	3859	6235	6101	5529	1559	11,305	11,519	23,069
1800 mg	3706	5988	6213	5631	1631	11826	11,550	23,446
13% control	3451	5576	5749	5211	1504	10912	10,704	21,699
66% control	2410	3894	3857	3496	991	7189	7258	14,578
1200 mg	2695	4355	4458	4038	1161	8427	8314	16,820
13% control	2537	4099	4170	3777	1083	7860	7790	15,736
66% control	1892	3056	2995	2713	765	5551	5652	11,320

*Based on RR associated with diuretic use; †Based on RR associated with diuretic use and new congestive heart failure (CHF) hospitalization data. MI Myocardial infarction

TABLE 2
Estimated proportion of all cardiovascular events in Canada prevented by various reductions in sodium intake

	Hypertension control rate	2400 mg/day sodium reduction	1800 mg/day sodium reduction	1200 mg/day sodium reduction
AMI	Similar response*	11	8	6
	13% control†	11	7	5
	66% control	8	5	4
Stroke	Similar response	17	12	9
	13% control	16	11	8
	66% control	12	7	6
Heart failure	Similar response	30	21	15
	13% control	28	19	14
	66% control	20	13	10
Total events	Similar response	19	13	9
	13% control	18	12	9
	66% control	13	8	6

*All hypertensive patients having similar response to sodium restriction; †Reduction in blood pressure in controlled hypertensive patients was assumed to be similar to that of normotensive patients, assuming either a 13% control rate or a 66% control rate. AMI Acute myocardial infarction



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