

## הודעה על החמרה (מידע בטיחות)

תאריך: 08.08.2012

שם תכשיר באנגלית: Stalevo

50/12.5/200 mg, 75/18.75/200 mg, 100/25/200 mg, 125/31.25/200 mg, 150/37.5/200mg, 200/50/200mg

מספר רישום: [31105, 32962, 31106, 32963, 31107, 31768]

שם בעל הרישום: נוברטיס פארמה סרויסס איי ג'י

טקסט שחור – טקסט מאושר  
טקסט עם קו תחתני – הוספת טקסט לעלון המאושר  
טקסט עם קו חוצה – מחיקת טקסט מהעלון המאושר  
טקסט המסומן בצהוב – טקסט המהווה החמרה

השינויים בעלון מסומנים על רקע צהוב

בעלון לרופא

פרטים על השינויים המבוקשים		
טקסט חדש	טקסט נוכחי	פרק בעלון
<p><u>Levodopa/carbidopa may cause false positive result when a dipstick is used to test for urinary ketone and this reaction is not altered by boiling the urine sample. The use of glucose oxidase methods may give false negative results for glycosuria.</u></p>		Special warnings and precautions for use
<p><u><b>a. Summary of the safety profile</b></u>  <u>The most frequently reported adverse reactions with Stalevo are dyskinesias occurring in approximately 19% of patients; gastrointestinal symptoms including nausea and diarrhoea occurring in approximately 15% and 12% of patients, respectively; muscle, musculoskeletal and connective tissue pain occurring in approximately 12% of patients; and harmless reddish-brown discolouration of urine (chromaturia) occurring in approximately 10% of patients. Serious events of gastrointestinal haemorrhage (uncommon) and angioedema (rare) have been identified from the clinical trials with Stalevo or entacapone combined with levodopa/DDC inhibitor. Serious hepatitis with mainly cholestatic features, rhabdomyolysis and neuroleptic malignant syndrome may occur with Stalevo although no cases have been identified from the clinical trial data.</u></p> <p><u><b>b. Tabulated list of adverse reactions</b></u>  <u>The following adverse reactions, listed in Table 1, have been accumulated both from a pooled data of eleven double-blind clinical trials consisting of 3230 patients (1810 treated with Stalevo or entacapone combined with levodopa/DDC inhibitor, and 1420 treated with placebo combined with levodopa/DDC inhibitor or</u></p>	<p>The following section describes the adverse reactions reported for levodopa/carbidopa and for entacapone used in combination with levodopa/DDC inhibitor.</p> <p><b>Levodopa / carbidopa</b></p> <p>Undesirable effects that occur frequently with levodopa/carbidopa are those due to the central neuropharmacological activity of dopamine. These reactions can usually be diminished by levodopa dosage reduction. The most common adverse reactions are dyskinesias including choreiform, dystonic and other involuntary movements. Muscle twitching and blepharospasm may be taken as early signs to consider levodopa dosage reduction. Nausea, also related to enhanced central dopaminergic activity, is a common adverse effect of levodopa/carbidopa. Other adverse reactions associated with levodopa/carbidopa therapy are mental changes, including paranoid ideation and psychotic episodes; depression, with or without development of suicidal tendencies; and cognitive dysfunction. Adding of entacapone to levodopa/DDC inhibitor therapy (carbidopa or benserazide), i.e. initiation of Stalevo treatment in an entacapone naive patient, may aggravate some of these mental changes (see Table 1, Psychiatric disorders).</p> <p>Less frequent adverse reactions of levodopa/carbidopa therapy are irregular heart rhythm and/or palpitations, orthostatic hypotensive episodes,</p>	Undesirable effects

<p><a href="#">cabergoline combined with levodopa/ DDC inhibitor</a>), and from the post-marketing data since the introduction of <a href="#">entacapone into the market for the combination use of entacapone with levodopa/DDC inhibitor</a>. Adverse reactions are ranked under headings of frequency, the most frequent first, using the following convention: Very common (<math>\geq 1/10</math>); common (<math>\geq 1/100</math> to <math>&lt; 1/10</math>); uncommon (<math>\geq 1/1,000</math> to <math>&lt; 1/100</math>); rare (<math>\geq 1/10,000</math> to <math>&lt; 1/1,000</math>), very rare (<math>&lt; 1/10,000</math>), not known (cannot be estimated from the available data, since no valid estimate can be derived from clinical trials or epidemiological studies).</p> <p><b>Table 1: Adverse reactions</b></p> <p><b>Blood and lymphatic system disorders</b></p> <p><b>Common:</b>     <b>Anaemia</b></p> <p><b>Uncommon:</b>   <b>Thrombocytopenia</b></p> <p><b>Metabolism and nutrition disorders</b></p> <p><b>Common:</b>     <b>Weight decreased*, decreased appetite*</b></p> <p><b>Psychiatric disorders</b></p> <p><b>Common:</b>     <b>Depression, hallucination, confusional state*, abnormal dreams*, anxiety, insomnia,</b></p> <p><b>Uncommon :</b>   <b>Psychosis, agitation*</b></p> <p><b>Not known:</b>   <b>Suicidal behaviour</b></p> <p><b>Nervous system disorders</b></p> <p><b>Very common:</b>       <b>Dyskinesia*</b></p> <p><b>Common:</b>     <b>Parkinsonism aggravated (e.g. bradykinesia)*, tremor, on and off phenomenon, dystonia, mental impairment (e.g. memory impairment, dementia), somnolence, dizziness*, headache</b></p> <p><b>Not known:</b>   <b>Neuroleptic malignant syndrome*</b></p> <p><b>Eye disorders</b></p> <p><b>Common:</b>     <b>Blurred vision</b></p> <p><b>Cardiac disorders</b></p> <p><b>Common:</b>     <b>Ischemic heart disease events other than myocardial infarction (e.g. angina pectoris)**, irregular heart rhythm</b></p> <p><b>Uncommon:</b>   <b>Myocardial infarction**</b></p> <p><b>Vascular disorders:</b></p> <p><b>Common:</b>     <b>Orthostatic hypotension, hypertension</b></p> <p><b>Uncommon:</b>   <b>Gastrointestinal haemorrhage</b></p>	<p>bradykinetic episodes (the 'on-off' phenomenon), anorexia, vomiting, dizziness, and somnolence. Gastrointestinal bleeding, development of duodenal ulcer, hypertension, phlebitis, leucopenia, haemolytic and non-haemolytic anaemia, thrombocytopenia, agranulocytosis, chest pain, dyspnoea and paraesthesia have occurred rarely with levodopa/carbidopa. Convulsions have occurred rarely with levodopa/carbidopa; however a causal relationship to levodopa/carbidopa therapy has not been established. Parkinson's disease patients treated with dopamine agonists and other dopaminergic treatments including Stalevo, especially at high doses, have been reported as exhibiting signs of pathological gambling, increased libido and hypersexuality, generally reversible upon reduction of the dose or treatment discontinuation.</p> <p>Other undesirable effects that have been reported with levodopa and may, therefore, also be potential adverse reactions of Stalevo, include:</p> <p>Metabolism and nutrition disorders: Weight gain or loss, oedema.</p> <p>Psychiatric disorders: Confusion, insomnia, nightmares, hallucinations, delusions, agitation, anxiety, euphoria.</p> <p>Nervous system disorders: Ataxia, numbness, increased hand tremor, muscle twitching, muscle cramp, trismus, activation of latent Horner's syndrome, falling and gait abnormalities.</p> <p>Eye disorders: Diplopia, blurred vision, dilated pupils, oculogyric crises.</p> <p>Gastro-intestinal disorders: Dry mouth, bitter taste, sialorrhoea, dysphagia, bruxism, hiccups, abdominal pain and distress, constipation, diarrhoea, flatulence, burning sensation of the tongue.</p> <p>Skin and subcutaneous tissue disorders: Flushing, increased sweating, dark sweat, rash, hair loss.</p> <p>Renal and urinary disorders: Urinary retention, urinary incontinence, dark urine, priapism.</p> <p>Miscellaneous: Weakness, faintness, fatigue, headache, hoarseness, malaise, hot flushes, sense of stimulation, bizarre breathing patterns, neuroleptic malignant syndrome, malignant melanoma.</p> <p><b>Entacapone</b></p> <p>The most frequent adverse reactions caused by entacapone relate to the increased dopaminergic activity and occur most commonly at the beginning of the</p>	
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<p><u>Respiratory, thoracic and mediastinal disorders</u></p> <p><u>Common: Dyspnoea</u></p> <p><u>Gastrointestinal disorders</u></p> <p><u>Very common: Diarrhoea*, nausea*</u></p> <p><u>Common: Constipation*, vomiting*, dyspepsia, abdominal pain and discomfort*, dry mouth*</u></p> <p><u>Uncommon: Colitis*, dysphagia</u></p> <p><u>Hepatobiliary disorders</u></p> <p><u>Uncommon: Hepatic function test abnormal*</u></p> <p><u>Not known: Hepatitis with mainly cholestatic features (see section 4.4)*</u></p> <p><u>Skin and subcutaneous tissue disorders</u></p> <p><u>Common: Rash*, hyperhidrosis</u></p> <p><u>Uncommon: Discolourations other than urine (e.g. skin, nail, hair, sweat)*</u></p> <p><u>Rare: Angioedema</u></p> <p><u>Not known: Urticaria*</u></p> <p><u>Musculoskeletal and connective tissue disorders</u></p> <p><u>Very common: Muscle, musculoskeletal and connective tissue pain*</u></p> <p><u>Common: Muscle spasms, arthralgia</u></p> <p><u>Not known: Rhabdomyolysis*</u></p> <p><u>Renal and urinary disorders</u></p> <p><u>Very common: Chromaturia*</u></p> <p><u>Common: Urinary tract infection</u></p> <p><u>Uncommon: Urinary retention</u></p> <p><u>General disorders and administration site conditions</u></p> <p><u>Common: Chest pain, peripheral oedema, fall, gait disturbance, asthenia, fatigue</u></p> <p><u>Uncommon: Malaise</u></p> <p><u>*Adverse reactions that are mainly attributable to entacapone or are more frequent (by the frequency difference of at least 1% in the clinical trial data) with entacapone than levodopa/DDC inhibitor alone. See section c.</u></p> <p><u>**The incidence rates of myocardial infarction and other ischemic heart disease events (0.43% and 1.54%, respectively) are derived from an analysis of 13 double-blind studies involving 2082 patients with end-of-dose motor fluctuations receiving entacapone.</u></p> <p><b><u>c. Description of selected adverse reactions</u></b></p>	<p>treatment. Reduction of levodopa dosage decreases the severity and frequency of the reactions. The other major class of adverse reactions are gastrointestinal symptoms, including for example nausea, vomiting, abdominal pain, constipations and diarrhoea. Urine may be discoloured reddish-brown by entacapone, but this is a harmless phenomenon.</p> <p>The following adverse reactions, listed in the table below, have been accumulated both from clinical studies with entacapone as an adjunct to levodopa/DDC inhibitor and since the introduction of entacapone into the market for the combination use of entacapone with levodopa/DDC inhibitor. Adverse reactions are ranked under headings of frequency, the most frequent first, using the following convention: Very common (<math>\geq 1/10</math>); common (<math>\geq 1/100</math>, <math>&lt; 1/10</math>); uncommon (<math>\geq 1/1000</math>, <math>&lt; 1/100</math>); rare (<math>\geq 1/10,000</math>, <math>&lt; 1/1000</math>); very rare (<math>&lt; 1/10,000</math>), not known (cannot be estimated from the available data, since no valid estimate can be derived from clinical trials or epidemiological studies). Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.</p> <p><b>Table: Adverse reactions from clinical studies with entacapone as an adjunct to levodopa/DDC inhibitor and from post-marketing experience</b></p> <p>Psychiatric disorders</p> <p>Common: Insomnia, hallucinations, confusion, nightmares, agitation</p> <p>Nervous system disorders</p> <p>Very common: Dyskinesia, Parkinsonism aggravated</p> <p>Common: Dizziness, dystonia, hyperkinesia</p> <p>Cardiac disorders</p> <p>Common Ischemic heart disease events other than myocardial infarction* (e.g. angina pectoris)</p> <p>Uncommon Myocardial infarction*</p> <p>Gastrointestinal disorders</p> <p>Very common: Nausea</p> <p>Common: Diarrhoea, abdominal pain, dry mouth, constipation, vomiting</p> <p>Very rare: Anorexia, colitis</p> <p>Hepato- biliary disorders</p> <p>Rare: Hepatic function tests abnormal</p> <p>Not known Hepatitis with mainly cholestatic features</p> <p>Skin and subcutaneous tissue disorders</p> <p>Rare Erythematous or maculopapular rash</p> <p>Very rare Urticaria</p> <p>Not known Skin, hair, beard and nail discolourations</p>
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<p>Adverse reactions that are mainly attributable to entacapone or are more frequent with entacapone than levodopa/DDC inhibitor alone are indicated with an asterisk in Table 1, section 4.8b. Some of these adverse reactions relate to the increased dopaminergic activity (e.g. dyskinesia, nausea and vomiting) and occur most commonly at the beginning of the treatment. Reduction of levodopa dose decreases the severity and frequency of these dopaminergic reactions. Few adverse reactions are known to be directly attributable to the active substance entacapone including diarrhoea and reddish-brown discolouration of urine. Entacapone may in some cases cause also discolouration of e.g. skin, nail, hair and sweat. Other adverse reactions with an asterisk in Table 1, section 4.8b are marked based on either their more frequent occurrence (by the frequency difference of at least 1%) in the clinical trial data with entacapone than levodopa/DDCI alone or the individual case safety reports received after the introduction of entacapone into the market.</p> <p>Convulsions have occurred rarely with levodopa/carbidopa; however a causal relationship to levodopa/carbidopa therapy has not been established.</p> <p>Parkinson's disease patients treated with dopamine agonists and other dopaminergic treatments such as Stalevo, especially at high doses, have been reported as exhibiting signs of pathological gambling, increased libido, hypersexuality and other urges, generally reversible upon reduction of the dose or treatment discontinuation. Entacapone in association with levodopa has been associated with isolated cases of excessive daytime somnolence and sudden sleep onset episodes.</p>	<p>Renal and Urinary disorders Very common: Urine discolouration General disorders and administration site conditions Common: Fatigue, sweating increased, fall Uncommon Weight decrease</p> <p>*The incidence rates of myocardial infarction and other ischemic heart disease events (0.43% and 1.54%, respectively) are derived from an analysis of 13 double-blind studies involving 2082 patients with end-of-dose motor fluctuations receiving entacapone.</p> <p>Entacapone used in combination with levodopa has been associated with isolated cases of excessive daytime somnolence and sudden sleep onset episodes (see section 4.7 Effects on ability to drive and use machines). Isolated cases of neuroleptic malignant syndrome (NMS) have been reported, especially following abrupt reduction or discontinuation of entacapone and other dopaminergic medications. Isolated cases of rhabdomyolysis have been reported. Isolated cases of angiodema have been reported after initiation of Stalevo.</p> <p><b>Laboratory tests</b> The following laboratory abnormalities have been reported with levodopa/carbidopa treatment and should, therefore, be borne in mind when treating patients with Stalevo: Commonly, levels of blood urea nitrogen, creatinine, and uric acid are lower during administration of levodopa/carbidopa than with levodopa alone. Transient abnormalities include elevated values of blood urea, AST (SGOT), ALT (SGPT), LDH, bilirubin, and alkaline phosphatase. Decreased haemoglobin, haematocrit, elevated serum glucose and white blood cells, bacteria and blood in the urine have been reported. Positive Coombs' tests have been reported, both for levodopa/carbidopa and for levodopa alone, but haemolytic anaemia is extremely rare. Levodopa/carbidopa may cause false positive result when a dipstick is used to test for urinary ketone; this reaction is not altered by boiling the urine sample. The use of glucose oxidase methods may give false negative results for glycosuria.</p>	
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פרטים על השינויים המבוקשים		
פרק בעלון	טקסט נוכחי	טקסט חדש
מתי אין להשתמש בתרופה	אם את מיניקה אם ידועה לך רגישות ללבדופה, קרבידופה, או אנטקפון או לכל אחד ממרכיבי התרופה	אם הנך אלרגית (רגישות יתר) ידועה לך רגישות ללבדופה, קרבידופה, או אנטקפון או לכל אחד ממרכיבי התרופה
אזהרות		אם יש לך חוסר תיאבון מתקדם, חולשה, תשישות, וירידה במשקל תוך פרק זמן קצר יחסית פנה/י לרופא.  הנקה יש לידע את הרופא אם את מיניקה. אין להיניק במהלך הטיפול בסטאלבו.
תופעות לוואי		אם הנך חש/ה אחת או יותר מתופעות הלוואי האלה יש לפנות לרופא בהקדם האפשרי.  תופעות לוואי שכיחות ביותר <ul style="list-style-type: none"><li>כאב שרירים</li><li>שלשול</li></ul> תופעות לוואי שכיחות <ul style="list-style-type: none"><li>קצב לב לא סדיר</li><li>לחץ דם גבוה</li><li>עקצוץ או חוסר תחושה;</li><li>כאבי בטן וחוסר נוחות בבטן;</li><li>צרבת; שלשול;</li><li>חלומות לא רגילים כולל סיוטי לילה; תחושת עצבנות;</li><li>שינויים נפשיים, כולל בעיות בזכרון או בחשיבה; תסמינים פרנואידים ופסיכוטיים; חרדה ודכאון (יתכן עם מחשבות אובדניות) ובעיות זיכרון וחשיבה;</li><li>נפילות תכופות יותר; הליכה לקויה; איבוד כוח ואנרגיה</li><li>גירוד ופריחות</li><li>התכווצויות שרירים; התכווצויות שרירים לא רצוניות; נפיחות של הרגליים</li><li>הפרעות בראייה; ראייה מטושטשת</li><li>אנמיה; ירידה בתאבון; ירידה במשקל</li><li>כאב ראש; כאב פרקים</li><li>דלקת בדרכי השתן</li></ul> תופעות לוואי בלתי שכיחות <ul style="list-style-type: none"><li>קצב לב לא סדיר;</li><li>כיבים;</li><li>לחץ דם גבוה; בדיקות תיפקודי כבד חריגות</li></ul>
	תופעות לוואי שכיחות <ul style="list-style-type: none"><li>עקצוץ או חוסר תחושה;</li><li>כאבי בטן; שלשול;</li><li>סיוטי לילה; תחושת עצבנות;</li><li>שינויים נפשיים, כולל תסמינים פרנואידים ופסיכוטיים, דכאון (יתכן עם מחשבות אובדניות) ובעיות זיכרון וחשיבה;</li><li>נפילות תכופות יותר;</li><li>גירוד ופריחות;</li><li>התכווצויות שרירים;</li><li>הפרעות בראייה;</li></ul> תופעות לוואי בלתי שכיחות <ul style="list-style-type: none"><li>קצב לב לא סדיר;</li><li>כיבים;</li><li>לחץ דם גבוה;</li></ul>	

<ul style="list-style-type: none"> <li>• <u>תסמינים פסיכויטטיים ; תחושת עצבנות</u></li> <li>• <u>דלקת המעי הגס (colitis)</u></li> <li>• <u>שינוי צבע העור, הציפורניים, השיער והזיעה</u></li> <li>• <u>עייפות/יתכן</u></li> <li>• <u>עקב שינויים בתאי הדם, עלפון, זיהומים, דימום,</u></li> <li>• <u>שינויים בספירת תאי הדם אשר עלולים לגרום לדימום</u></li> <li>• <u>קשיים בבליעה</u></li> <li>• <u>חוסר יכולת לתת שתן</u></li> <li>• <u>הרגשת חולי באופן כללי</u></li> <li>• <u>דלקת בורידים ברגליים,</u></li> <li>• <u>עוויתות,</u></li> </ul> <p><b>תופעות לוואי נוספות</b></p> <ul style="list-style-type: none"> <li>• <u>צהבת (דלקת הכבד)</u></li> <li>• <u>גירוד</u></li> </ul>	<ul style="list-style-type: none"> <li>• עייפות (יתכן עקב שינויים בתאי הדם), עלפון, זיהומים ; דימום ;</li> <li>• דלקת בורידים ברגליים ;</li> <li>• עוויתות ;</li> </ul>	
<ul style="list-style-type: none"> <li>• <u>השרירים שלך הופכים נוקשים מאוד או מתעוותים בחוזקה, יש לך רעידות, עצבנות, בלבול, חוס, דופק מהיר או תנודות קיצוניות בלחץ הדם שלך. אלה יכולים להיות סימנים של Neuroleptic Malignant Syndrome (NMS), תגובה חמורה נדירה לתרופות המשמשות לטיפול בהפרעות של מערכת העצבים המרכזית) או רבדומיוליזיס (מחלת שריר חמורה נדירה).</u></li> </ul>		<p><b>תופעות המחייבות התייחסות מיוחדת</b></p>
<p><u>יש להרחיק מהישג ידם ותחום ראיתם של ילדים.</u></p>		<p><b>אחסנה</b></p>