



**This is an update to the FDA Drug Safety Communication: Ongoing Safety Review of Stalevo (entacapone/carbidopa/levodopa) and Possible Development of Prostate Cancer issued on March 31, 2010**

## FDA Drug Safety Communication

FDA review finds no increased risk of prostate cancer with Parkinson's disease medicines containing entacapone (Comtan, Stalevo)

### Safety Announcement

**[08-13-2019]** A U.S. Food and Drug Administration (FDA) review of additional data found no increased risk of prostate cancer with the use of entacapone to treat Parkinson's disease. We conducted this review after an earlier trial<sup>1</sup> suggested this possible risk. As a result, our recommendations for using Comtan (entacapone) and Stalevo (a combination of entacapone, carbidopa, and levodopa) will remain the same in the [prescribing information](#).

We alerted the public in [March 2010](#) that we were aware of a clinical trial<sup>1</sup> suggesting a possible increased risk of prostate cancer with the entacapone component of Stalevo. We subsequently required the Stalevo manufacturer, Novartis, to conduct a study<sup>2</sup> to further evaluate this potential risk. We also studied this issue independently using data from the Department of Veterans Affairs health care system.<sup>3</sup> Based on these additional studies, we concluded that entacapone use is not associated with an increased risk of prostate cancer (see Data Summary).

Medicines that contain entacapone with carbidopa and levodopa have been shown to effectively treat symptoms of Parkinson's disease such as muscle stiffness, tremors, spasms, and poor muscle control. These medicines have been approved and on the market for almost 20 years. The combination of entacapone with carbidopa and levodopa in Stalevo has been shown to reduce end-of-dose "wearing-off" in patients with Parkinson's disease to a greater degree than with entacapone alone or with the two-drug combination of carbidopa and levodopa.

**Health care professionals** should follow standard prostate cancer screening recommendations for patients.

**Patient and caregivers** should continue to take your medicine as prescribed. Talk to your health care professionals if you have any questions or concerns.

To help FDA track safety issues with medicines, we urge patients and health care professionals to report side effects involving entacapone-containing products or other medicines to the FDA MedWatch program, using the information in the “Contact FDA” box at the bottom of the page.

### Data Summary

An unexpected finding in the Stalevo Reduction in Dyskinesia Evaluation – Parkinson's Disease (STRIDE-PD) trial was that a greater number of patients taking Stalevo were observed to have prostate cancer compared to those taking carbidopa/levodopa.<sup>1</sup> STRIDE-PD evaluated the time to onset of dyskinesia, or difficulty controlling voluntary movement, in patients with Parkinson's disease taking Stalevo compared to those taking only carbidopa/levodopa. To further assess this safety concern, in 2011 we required the manufacturer of Stalevo, Novartis, to conduct an observational cohort study<sup>2</sup> in patients with Parkinson's disease, comparing the incidence rate of prostate cancer in a cohort of patients treated with entacapone plus a conventional PD treatment of dopa decarboxylase inhibitor/levodopa (DDCI/LD) with a cohort of patients treated with DDCI/LD plus either a dopamine agonist or a monoamine oxidase B inhibitor.

The study involved 11,396 men in Finland with Parkinson's disease, 1,141 of whom received entacapone. A total of 359 prostate cancer cases occurred during an average follow-up time of 4.6 years, with 89 prostate cancer deaths during an average follow-up time of 4.7 years. Treatment with DDCI/LD with add-on entacapone (Group 1) was not associated with an increased risk of prostate cancer (hazard ratio [HR]=1.05; 95% confidence interval [CI]=0.76-1.44) or prostate cancer mortality (HR=0.93; 95% CI: 0.43-1.98) compared to treatment with DCCI/LD without add-on entacapone (Group 2). Similarly, evaluation of the secondary objectives showed that longer cumulative treatment with entacapone was not associated with an increased risk of prostate cancer or prostate cancer death. The HR estimates for patients with more than 360 days cumulative treatment with entacapone were 0.82 (95% CI: 0.56-1.18) for prostate cancer incidence and 1.27 (95% CI: 0.59-2.72) for prostate cancer death, respectively, compared to patients with no entacapone treatment.

Table 1. Risks of Prostate Cancer (PC) Development and Mortality – Results from Finnish Study

	Outcome <sup>+</sup>	Adj Hazard Ratio	95% Confidence Interval
Group 1:Group 2	PC incidence	1.05	0.76-1.44
Group 1:Group 2	PC mortality	0.93	0.43-1.98
Cumulative treatment >360 days	PC incidence	0.82	0.56-1.18

Cumulative treatment >360 days	PC mortality	1.27	0.60-2.72
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\*Exposure to conventional PD treatment of dopa decarboxylase inhibitor/levodopa (DDCI/LD) with or without add-on entacapone

The study had limitations in the design and how the results were analyzed. The main limitations included the short period of time that Stalevo had been available in Finland compared to the long latency period of prostate cancer, the potential for decreased surveillance for prostate cancer in male patients with advanced Parkinson's disease, and lack of information pertaining to important factors such as family history of prostate cancer and prior screenings for prostate cancer.

The FDA and Veterans Affairs (VA) Center for Medication Safety also conducted a retrospective cohort study<sup>3</sup> of 17,666 U.S. male veterans with Parkinson's disease treated with levodopa-carbidopa (n=5,257), comparing add-on entacapone therapy to the control cohort, which received add-on therapy with a dopamine agonist or monoamine oxidase B inhibitor (n=12,409). Patients were followed for occurrence of prostate cancer using data from the VA cancer registry. Mean follow-up time was 3.1 years and 4.0 years, respectively, in the entacapone and control cohorts. Twenty-three prostate cancer cases occurred in the entacapone cohort and 97 in the control cohort. There was no difference in risk of prostate cancer between the cohorts for increased duration of cumulative entacapone treatment of more than 2 years (adjusted HR=1.08; 95% CI: 0.46-2.51). Time since starting drug therapy and cumulative dose also did not suggest a difference in prostate cancer risk between the cohorts.

The low overall incidence rate of 1.8 cases of prostate cancer per 1,000 person-years compared to the age-adjusted rate of 1.3 per 1,000 U.S. males in the general population may reflect a possible bias in cancer ascertainment after Parkinson's disease was diagnosed. This may be partly due to a decrease in screening for prostate cancer in the U.S., particularly in men with chronic medical conditions. This may have led to a potential decrease in prostate cancer detection, a limitation of the study.

## References

1. Stocchi F, Rascol O, Kieburtz K, Poewe W, Jankovic J, Tolosa E, Barone P, Lang AE, Olanow CW. Initiating levodopa/carbidopa therapy with and without entacapone in early Parkinson disease: the STRIDE-PD study. *Ann Neurol* 2010 Jul; 68(1):18-27.
2. Korhonen P, Haukka J, Kuoppamaki M, Ellmen J, Aho V, Vahteristo M. The risk of developing prostate cancer in entacapone and levodopa/DDCI users compared to levodopa/DDCI users without entacapone – A nation-wide retrospective register-based study. EPID Research Oy, Tekniikantie, Finland. June 25, 2013.

3. Major JM, Dong D, Cunningham F, et al. Entacapone and prostate cancer in Parkinson's disease patients: A large Veterans Affairs healthcare system study. *Parkinsonism and Relat Disord* 2018 Aug;53:46-52.

### **Related Information**

- [Parkinson's Disease](#)
- [Prostate Cancer Screening](#)
- [The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective](#)
- [Think It Through: Managing the Benefits and Risks of Medicines](#)