DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Martina Struck, PhD
Associate Director, Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, New Jersey 07936

RE: **NDA 20-796**
Comtan® (entacapone) Tablets
MACMIS# 10390

Dear Dr. Struck:

This letter is to notify you that the Division of Drug Marketing, Advertising, and Communications (DDMAC) has identified "Extend the Reach: A Measurable Outcomes Program" for Comtan® (entacapone) Tablets to be misleading and in violation of the Federal Food, Drug, and Cosmetic Act and applicable regulations.

Specifically, the "Extend the Reach Patient Starter Kit" makes the following misleading statements:

- "Extend the Reach is designed to allow you to be part of a nationwide assessment of the impact of COMTAN® (entacapone) therapy on your quality of life."

- "In a recent survey, 1168 people with PD who took COMTAN along with their levodopa/carbidopa therapy reported improvements in their overall well-being and mood when compared with levodopa/carbidopa therapy alone."

These statements imply that Comtan therapy impacts patient quality of life, overall well-being, and mood, where these outcomes have not been demonstrated with substantial evidence from adequate and well-controlled studies using well-developed and validated measures.

We therefore object to the use of the claims above in "Extend the Reach: A Measurable Outcomes Program." In addition, the program is misleading because it implies that the data will be used to assess the clinical benefit of Comtan therapy. An uncontrolled study design is not able to produce adequate evidence to support a claim of clinical benefit. To address this objection, we recommend that you do the following:

1. Immediately discontinue the use of the "Extend the Reach Patient Starter Kit" and any other promotional material with the same or similar messages.

2. Respond to this letter within ten days. Your response should include a statement of your intent to comply with the above, a list of promotional materials with the same or similar issues, and your methods for discontinuing these promotional materials.

If you have any questions or comments, please contact me by facsimile at (301) 594-6759, or at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-42, Room 17B-23, 5600 Fishers Lane Rockville, MD 20857. We remind you that only written communications are considered official.

Sincerely,

{See appended electronic signature page}

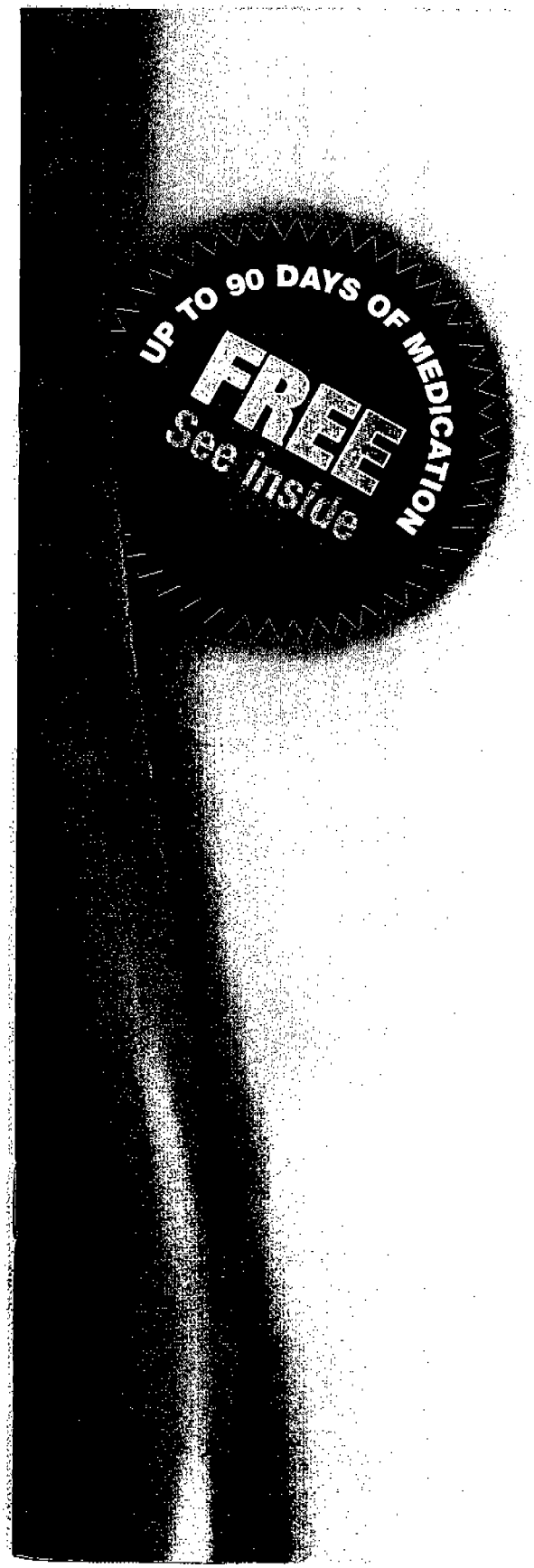
Elaine J. Hu, R.Ph.
Regulatory Review Officer
Evidence Review Branch
Division of Drug Marketing,
Advertising, and Communications

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Elaine J. Hu
10/3/01 03:40:52 PM

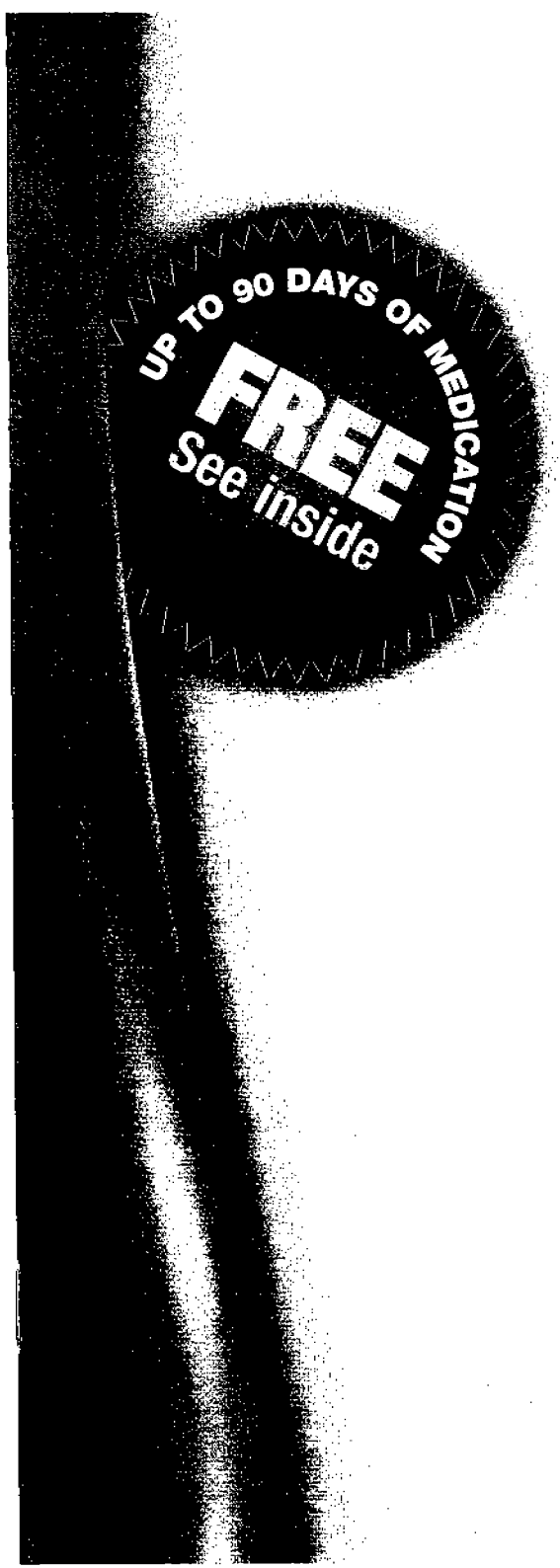
Voucher for up to a 90-day supply free—Details inside



EXTEND *the reach*
A Measurable Outcomes Program

Patient Starter Kit

Sponsored by the
National Parkinson Foundation



EXTEND *the reach*
A Measurable Outcomes Program

COMTAN extends levodopa benefits, helping patients with Parkinson's disease stay active longer.

COMTan®

EXTEND *the reach*
A Measurable Outcomes Program

Thank you again for taking part in the Extend the Reach program

If you have any questions about your participation in this program, call **1-800-678-4611.** If you have any questions about COMTAN, please consult your doctor or call **1-888-NOW-NOVA** (1-888-669-6682). You can also log on to the COMTAN Web site at: **www.comtan.com**

COMTan®

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A Measurable Outcomes Program

On Behalf of the National Parkinson Foundation:

Welcome to the Extend the Reach program—a service from your physician and Novartis Pharmaceuticals Corporation. This exclusive program has been specially developed for people just like you, who have Parkinson's disease and are currently taking levodopa/carbidopa therapy. **Extend the Reach** is designed to allow you to be part of a nationwide assessment of the impact of COMTAN® (entacapone) therapy on your quality of life. In exchange for your honest feedback, you will receive a complimentary 90-day supply of COMTAN therapy, in addition to your current levodopa/carbidopa therapy (ie, Sinemet®,* Sinemet CR®,* or other levodopa/carbidopa preparations).

*Sinemet and Sinemet CR are registered trademarks of DuPont Pharma.

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A Measurable Outcomes Program

As a participant in this program, you have the opportunity to receive up to a 90-day supply of COMTAN® (entacapone) therapy plus your current levodopa/carbidopa therapy—free of charge.

All you need to do is complete 2 surveys—one before you start COMTAN therapy, and one after taking COMTAN therapy for 60 days. The questions on the surveys are very simple—they let you assess how you are feeling, as well as rate your ability to perform different activities throughout your day. The initial 60-day supply is available the day you agree to participate.

When you complete the second survey (after 60 days of COMTAN therapy), you will receive an ***additional*** 30-day supply of COMTAN and levodopa/carbidopa—for a total of 3 months of medication at no cost to you.

Bonus: To thank you for participating in the **Extend the Reach** program, you will also receive a copy of a new book entitled *Shaking Up Parkinson's* by Dr Abraham Lieberman, Medical Director of the National Parkinson Foundation (NPF).

Please see complete product information for COMTAN, available in this kit.

EXTEND *the reach* Participation Guidelines

A Measurable Outcomes Program

Your physician will get you started with everything you need to participate.

1. In your starter kit, you will find a participation form and baseline survey located in the back pocket.
   - Please complete both forms, place them in the postage-paid return envelope provided, and mail them to the NPF before you begin COMTAN® (entacapone) therapy
2. At your initial visit, your physician will provide you with a 60-day prescription for COMTAN therapy and for your regular levodopa/carbidopa therapy.
   - Your doctor will complete the 60-day pharmacy voucher, found on the baseline survey, and affix it to your COMTAN prescription
3. Be sure to schedule your 60-day follow-up visit.
   - To help you remember your follow-up visit, mark the time and date on the enclosed reminder magnet
4. Bring the prescriptions and the pharmacy voucher to your local pharmacy to redeem your 60-day supply of COMTAN and your usual levodopa/carbidopa medication—free of charge.

5. Approximately 45 days after starting the program, you will receive the follow-up survey, accompanied by a reminder letter and an additional 30-day pharmacy voucher.
   - Please complete the survey when you have finished all of your COMTAN therapy. This survey will let you rate the impact of COMTAN therapy on your quality of life

6. After completing your COMTAN therapy you'll need to return to the doctor's office for your follow-up visit. Remember to bring the follow-up survey with you.
   - Here, your doctor will provide you with an additional prescription for COMTAN and for your levodopa/carbidopa therapy
   - Your doctor will also complete the necessary information on the additional pharmacy voucher, located on the follow-up survey, and place it on the back of your new COMTAN prescription
   - You can then take your new prescriptions—along with your voucher—to your local pharmacy to have them filled

7. After your doctor's visit, please mail your completed follow-up survey to the NPF in the postage-paid return envelope provided.
   - For completing the follow-up survey, you will receive a copy of *Shaking Up Parkinson's*, a new book by Dr Abraham Lieberman, Medical Director of the National Parkinson Foundation

EXTEND *the reach*
A Measurable Outcomes Program

Participation Guidelines

Why you were chosen to participate in Extend the Reach

- COMTAN® (entacapone) Tablets are available for people with Parkinson's disease (PD) who take levodopa/carbidopa therapy and notice parkinsonian symptoms reappearing or returning before taking their next dose of levodopa/carbidopa—otherwise known as end-of-dose "wearing-off"
- Your doctor has prescribed COMTAN in conjunction with your current levodopa/carbidopa therapy to help you better control the signs and symptoms of PD

In this starter kit, you will find resources to help you while participating in the program.

About COMTAN Therapy

In the next few pages, you will read some of the most frequently asked questions about COMTAN therapy. If you have a question that isn't listed here, please consult your doctor.

Dosing Reminder Guide/Magnet

This starter kit also includes a daily dosing reminder guide to help you take your COMTAN therapy appropriately. Fill out the guide with your doctor and then use the enclosed magnet to attach the guide to your refrigerator. This guide will help you remember the right amount of medicine you need to take and the right times to take it.

EXTEND *the reach*
A Measurable Outcomes Program

About COMTAN Therapy

COMTAN® (entacapone) therapy is a medication for people with PD taking levodopa/carbidopa who notice the reappearance of parkinsonian symptoms before taking their next dose of levodopa/carbidopa.

COMTAN works with levodopa/carbidopa to help extend its benefits so that people with Parkinson's disease can stay active longer.

Here are some frequently asked questions about COMTAN therapy:

1. **Q. What is COMTAN?**

   A. COMTAN is a medication to help in the treatment of PD. COMTAN is a member of a class of medications called catechol O-methyltransferase (pronounced KAT-uh-kol oh-METH-uhl-trans-fur-ayse) inhibitors—more easily stated as COMT inhibitors. When taken properly, COMTAN works to make the benefits of levodopa/carbidopa therapy last longer, thereby helping you carry out everyday activities and tasks.

2. **Q. Why was COMTAN added to my daily medication schedule?**

   A. Your doctor may have prescribed COMTAN to help you get more benefit from your levodopa/carbidopa therapy. When added to levodopa/carbidopa therapy, COMTAN can help improve the amount of time that you spend in the "on" condition (a period of time when the patient is relatively free of PD symptoms), while reducing the amount of time that you spend in the "off" condition (a period of time when the patient experiences increased PD symptoms). This can mean a greater improvement in the control of PD symptoms, while helping you pursue activities of daily living and independence. Check with your doctor for the specific reasons that you were prescribed COMTAN.

3. **Q. How do COMTAN tablets work?**

   A. The COMT enzyme is a substance in the body that breaks down levodopa before it can get to the brain. By blocking the COMT enzyme, COMTAN helps more levodopa from each dose you take become available to the brain.

   When levodopa reaches the brain, it is converted into dopamine (DOPE-a-meen). Dopamine is the chemical that helps the brain control activities such as walking, talking, and moving. People who have PD don't produce enough dopamine. In addition, the cells in the brain that make dopamine aren't working properly. That's why you are taking levodopa/carbidopa medicine. Supplementing dopamine in the brain by taking levodopa can help control PD symptoms. And COMTAN can help ensure that more levodopa reaches the brain—enabling people to pursue daily tasks such as dressing, walking, and handling utensils.

4. **Q. When should COMTAN therapy be used?**

   A. Physicians may prescribe COMTAN for people with PD who are on levodopa/carbidopa therapy and notice that the benefits of the medication fade. For example, right before taking the next dose of levodopa/carbidopa, some people will notice that their symptoms come back. Known as levodopa "wearing-off," the return of symptoms means levodopa is losing its effectiveness. This is where COMTAN can help. COMTAN therapy can help extend the benefits of levodopa/carbidopa therapy, minimizing "wearing-off" and helping to control the symptoms of PD for a longer period of time. Importantly, in order for COMTAN to work, it must always be taken along with levodopa/carbidopa therapy.

5. **Q. How effective is COMTAN® (entacapone) therapy?**

   A. In clinical trials, COMTAN significantly improved the control of the symptoms of PD, prolonging the benefits of levodopa. Taking COMTAN helps more levodopa become available to the brain, so people with PD can experience better control of symptoms, for a longer period of time. In a recent survey, 1168 people with PD who took COMTAN along with their levodopa/carbidopa therapy reported improvements in their overall well-being and mood when compared with levodopa/carbidopa therapy alone. They also stated that they were better able to get dressed, communicate, and get around in public after COMTAN was added.

6. **Q. Can COMTAN be taken without levodopa/carbidopa medicine?**

   A. COMTAN has no effect on the symptoms of PD by itself. To get benefits from COMTAN, it must be taken along with your levodopa/carbidopa medicine. When taken this way, COMTAN extends the effects of levodopa/carbidopa, which means you will have better control of PD symptoms for a longer period of time.

7. **Q. Are there any side effects associated with COMTAN therapy?**

   A. COMTAN has been shown to cause few side effects, which may be easily managed. In clinical studies with COMTAN, among more than 1400 people with PD, the most commonly reported side effects were unwanted or uncontrolled movements (sometimes called dyskinesias). These side effects were related to levodopa/carbidopa therapy and were generally mild to moderate in severity. If you experience these

side effects, talk to your doctor—he or she can usually manage these side effects by lowering the levodopa/carbidopa dose.

Other side effects included upset stomach, diarrhea, urine discoloration, abdominal pain, dizziness, constipation, tiredness, and pain. While these are the most commonly reported side effects in the studies, this does not mean you will experience them while taking COMTAN. In rare instances, COMTAN may be associated with low blood pressure, muscular problems, high fevers, and severe diarrhea.

No liver tests are required with COMTAN use. However, COMTAN should be used with caution by people with existing liver problems because it is metabolized by the liver and will increase blood levels. If you experience any side effects, or have any questions about the medication you are taking, talk to your doctor.

To help you benefit the most from treatment, your doctor might have to reduce either the amount of levodopa/carbidopa therapy you take or the number of times you take it during the day. IMPORTANT: COMTAN and levodopa therapies should not be taken along with medications called nonselective monoamine oxidase (MAO) inhibitors, nor with selegiline at doses higher than 10 mg per day. Drugs that are broken down by the COMT enzyme (eg, isoproterenol, epinephrine) should be used with caution when taking COMTAN. You should not abruptly stop taking or reduce the amount of COMTAN or any other antiparkinsonian medication. Talk to your doctor about what you should do if you both decide to discontinue COMTAN therapy.

8. **Q. Is there anything else I should know about COMTAN® (entacapone) therapy?**

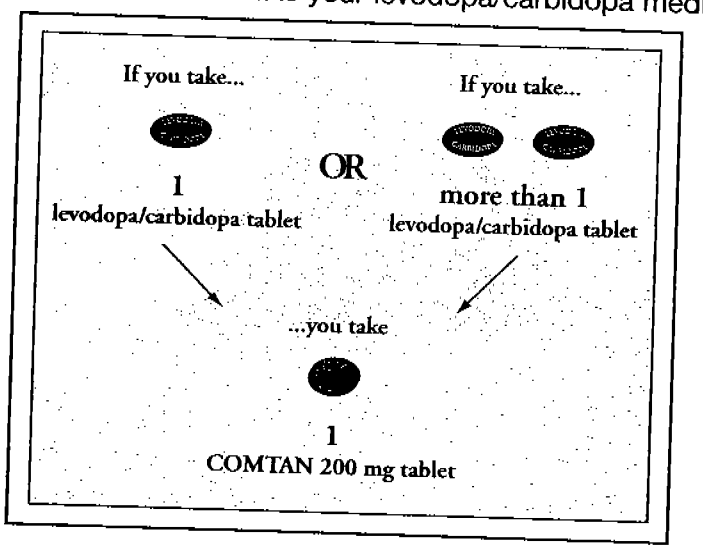
   A. In some people, COMTAN may cause the urine to change color—becoming brownish orange. This is a harmless side effect and is not a cause for concern.

9. **Q. How often should I take COMTAN?**

   A. For consistent benefits, take 1 COMTAN tablet every time you take your levodopa/carbidopa medicine. So whether you have to take 1 levodopa tablet or more than 1, at each administration simply take 1 COMTAN tablet along with your usual dose of levodopa/carbidopa medicine. You should not take more than 8 COMTAN tablets each day. Your doctor will provide you with specific instructions on how to take COMTAN. If you have any questions about taking COMTAN, talk to your doctor.

Taking your COMTAN tablets

When it's time to take your levodopa/carbidopa medicine...



10. Q. Can COMTAN be taken with food?

A. Yes. COMTAN can be taken with or without food.

11. Q. Can COMTAN be taken with a controlled-release form of levodopa/carbidopa?

A. Yes. In fact, COMTAN can be taken with either formulation of levodopa/carbidopa—regular or controlled release. In either case, COMTAN should be taken the same way: 1 COMTAN 200 mg tablet along with every administration of levodopa/carbidopa therapy.

12. Q. What if I miss a dose of COMTAN?

A. COMTAN should always be taken at the same time as your levodopa/carbidopa medicine. If a COMTAN dose is missed, do not double up. Simply wait until the next time you are supposed to take levodopa/carbidopa and take COMTAN along with your usual levodopa/carbidopa dose, as prescribed by your doctor. Talk to your doctor about what steps you can take in case more than 1 dose of COMTAN is missed.

13. Q. If my doctor changes my daily levodopa/carbidopa dose, will my COMTAN® (entacapone) dose change, too?

A. If your levodopa/carbidopa dose or the frequency of doses changes, your doctor will tell you how to continue taking COMTAN. If you have any questions or are uncertain about how to take COMTAN, how much to take, or when to take it, talk to your doctor. As with any prescription medication, COMTAN should be taken exactly as prescribed by your doctor.

14. Q. Can COMTAN be taken with other PD medications?

A. In clinical studies, there were no interactions reported when people used other PD medications along with COMTAN. However, COMTAN must not be used with certain medications, such as nonselective MAO inhibitors, nor with selegiline at doses greater than 10 mg per day. If you are taking any other medications, talk with your doctor before using COMTAN. To help ensure there will be no problems with COMTAN tablets and any other medications you may be taking, make a list of all your medications—prescription and over the counter—as well as the doses of each, and discuss them with your doctor.

15. Q. How long does it take before COMTAN starts working?

A. COMTAN begins working right away, helping to provide consistent control of symptoms. Remember: COMTAN works only when taken with levodopa/carbidopa therapy.

16. Q. How long should I take COMTAN?

A. You should take COMTAN in accordance with your doctor's instructions. For best results, stay on COMTAN until your doctor tells you to stop therapy.

17. Q. How should COMTAN be stored?

A. Don't store COMTAN near extreme cold or heat. It is best to store COMTAN tablets at room temperature—between 59°F and 86°F (15°C to 30°C).

18. Q. Where can I get more information about my treatment with COMTAN?

A. If you would like more information about COMTAN, speak with your doctor or pharmacist. You can also find more information about COMTAN at **www.comtan.com**.

19. Q. Where can I find additional information on Parkinson's disease and its treatment?

A. Today, more and more information on Parkinson's disease is available from a number of different organizations dedicated to Parkinson's disease research and treatments. A large amount of information is also available through the Internet. A brief list of some well-known organizations follows. If you have any questions about information you receive, please talk with your doctor.

EXTEND the reach
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The American Parkinson Disease Association, Inc. (APDA)
1-800-223-APDA (2732) *www.apdaparkinson.com*

The APDA sponsors support groups and symposia, provides information and referral centers, publishes a newsletter, and provides other educational materials.

National Parkinson Foundation, Inc. (NPF)
1-800-327-4545 *www.parkinson.org*

This foundation provides information and offers PD resources for physicians, patients, and caregivers.

Parkinson's Disease Foundation, Inc. (PDF)
1-800-457-6676 *www.pdf.org*

This foundation helps raise research funds, promotes the formation of support groups, and offers patient information, counseling, advocacy, and referral services.

The Michael J. Fox Foundation for Parkinson's Research
1-800-708-7644 *www.michaeljfox.com*

Founded by Michael J. Fox, this foundation is dedicated to helping find the cure for PD. It will aggressively identify the most promising research and actively raise funds to assure that the best PD research is supported.

The Parkinson's Institute
1-800-786-2958 *www.parkinsonsinstitute.org*

This institute operates a clinic and research facility, publishes a newsletter, and offers many other services for patients and their families.

Parkinson's Support Groups of America (PSGA)
1-301-937-1545

This organization promotes research; maintains a library; sponsors a speakers bureau, support groups, and an annual convention; and offers other services and programs for the public.

Please see complete product information for COMTAN®, available in this kit.

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A Measurable Outcomes Program

National Parkinson Foundation

The National Parkinson Foundation (NPF) is a nationwide, nonprofit organization that is dedicated to:

- Finding the cause and cure for PD and related neurodegenerative disorders through research
- Educating general medical practitioners to detect the early warning signs of PD
- Educating patients, their caregivers, and the general public
- Providing diagnostic and therapeutic services
- Improving the quality of life for patients and their caregivers

The NPF supports researchers; physicians; occupational, physical, and speech therapists; and psychological counseling. It also provides educational and medical information for patients with Parkinson's disease, their families, neurologists, and general medical practitioners. Through dedicated research, the goal of the NPF is to find the cause and cure of this disease and other neurologic disorders in our lifetime. Continued support will enable the NPF to expand their research activities, pursue additional clinical trials of new medications, and thereby assist the patients to maintain a more normal quality of life.

For more information about the National Parkinson Foundation, please visit ***www.parkinson.org***

COMTan® (entacapone) tablets

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How to Receive Your Complimentary Supply of Medication

1. Your physician will write prescriptions for COMTAN® and levodopa/carbidopa therapy and will affix the 60-day pharmacy voucher (found on the bottom of the baseline survey) to the back of your COMTAN prescription form.

2. Take the prescriptions to your pharmacy to receive a 60-day supply of COMTAN and levodopa/carbidopa therapy, at no charge.

3. After approximately 45 days of therapy, you will receive a follow-up survey in the mail. Please complete this survey once you have finished all your COMTAN medication, and bring it with you to your scheduled follow-up visit.

4. At this time, your doctor will write subsequent prescriptions for COMTAN and your usual levodopa/carbidopa therapy. Then, your doctor will complete and affix your second pharmacy voucher (found on the bottom of the follow-up survey) to your COMTAN prescription. This voucher is good for an additional 30-day supply of medication.

COMTan®
(entacapone) tablets

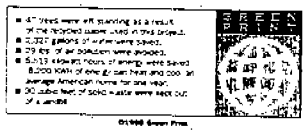
Enclosed you will find:

- Participation form
- Baseline survey

Before you begin COMTAN therapy, please complete and mail these forms in the postage-paid return envelope to the NPF.

All forms should be mailed to:

NPF
PO Box 310751
Boca Raton, FL 33431-9796



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EXTEND the reach
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COMTAN® Therapy:
Your Everyday Dosing Guide

Ask your doctor to help you fill out this chart. Then attach it to your refrigerator or bulletin board, or keep it where you keep your medicine. This way, you will always know the right amount of medicine you need to take and the right times you need to take it.

TIME	LEVODOPA/ CARBIDOPA	SINEMET® CR*	COMTAN®
1. AM PM			
2. AM PM			
3. AM PM			
4. AM PM			
5. AM PM			
6. AM PM			
7. AM PM			
8. AM PM			

*Sinemet CR is a registered trademark of DuPont Pharma.

Please see complete product information for COMTAN enclosed or by visiting the COMTAN Web site at: **www.comtan.com**. Additional dosing guide forms are also available at this Web site.

National Parkinson Foundation, Inc.

COMTan® (entacapone) tablets

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National Parkinson Foundation, Inc.

PATIENT PARTICIPATION FORM

Welcome to the Extend the Reach program. Please fill out the following information by printing clearly with blue or black ink.

Your Information

Last Name: _____ First Name: _____ Middle Initial: _____

Street Address: _____

City: _____ State: _____ ZIP: _____

Phone Number: ( ) _____

Date of Birth: ____/____/____ Gender: ☐ Male ☐ Female

Physician Information

Physician's First Name: _____ Last Name: _____

Phone Number: ( ) _____

Release of Information

I agree to participate in the **Extend the Reach** program. I understand that this program will allow me to receive COMTAN® (entacapone) Tablets and levodopa/carbidopa free of charge for up to 3 months. In return, I agree to complete the baseline survey and follow-up survey, during which I will answer questions about my well-being. I understand that my answers will be kept strictly confidential, will be pooled with other patients' responses, and may be shared anonymously with health care providers through various media.

Name (please print): _____

Signature: _____ Date: _____

NOVARTIS

Novartis Pharmaceuticals Corporation
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COMTan® (entacapone) tablets

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IF MAILED
IN THE
UNITED STATES

BUSINESS REPLY MAIL

FIRST-CLASS MAIL PERMIT 2413 BOCA RATON FL

POSTAGE WILL BE PAID BY ADDRESSEE

NPF
PO BOX 310751
BOCA RATON FL 33431-9796

Comtan®
(entacapone)
Tablets

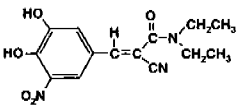
Rx only

Prescribing Information

DESCRIPTION

Comtan® (entacapone) is available as tablets containing 200-mg entacapone.

Entacapone is an inhibitor of catechol-*O*-methyltransferase (COMT), used in the treatment of Parkinson's Disease as an adjunct to levodopa/carbidopa therapy. It is a nitrocatechol-structured compound with a relative molecular mass of 305.29. The chemical name of entacapone is (E)-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)-N,N-diethyl-2-propenamide. Its empirical formula is $C_{14}H_{15}N_3O_5$ and its structural formula is:



The inactive ingredients of the Comtan tablet are microcrystalline cellulose, mannitol, croscarmellose sodium, hydrogenated vegetable oil, hydroxypropyl methylcellulose, polysorbate 80, glycerol 85%, sucrose, magnesium stearate, yellow iron oxide, red oxide, and titanium dioxide.

CLINICAL PHARMACOLOGY

Mechanism of Action: Entacapone is a selective and reversible inhibitor of catechol-*O*-methyltransferase (COMT).

In mammals, COMT is distributed throughout various organs with the highest activities in the liver and kidney. COMT also occurs in the heart, lung, smooth and skeletal muscles, intestinal tract, reproductive organs, various glands, adipose tissue, skin, blood cells, and neuronal tissues, especially in glial cells. COMT catalyzes the transfer of the methyl group of S-adenosyl-L-methionine to the phenolic group of substrates that contain a catechol structure. Physiological substrates of COMT include dopa, catecholamines (dopamine, norepinephrine, and epinephrine) and their hydroxylated metabolites. The function of COMT is the elimination of biologically active catechols and some other hydroxylated metabolites. In the presence of a decarboxylase inhibitor, COMT becomes the major metabolizing enzyme for levodopa, catalyzing the metabolism to 3-methoxy-4-hydroxy-L-phenylalanine (3-OMD) in the brain and periphery.

The mechanism of action of entacapone is believed to be through its ability to inhibit COMT and alter the plasma pharmacokinetics of levodopa. When entacapone is given in conjunction with levodopa and an aromatic amino acid decarboxylase inhibitor, such as carbidopa, plasma levels of levodopa are greater and more sustained than after administration of levodopa and an aromatic amino acid decarboxylase inhibitor alone. It is believed that at a given frequency of levodopa administration, these more sustained plasma levels of levodopa result in more constant dopaminergic stimulation in the brain, leading to greater effects on the signs and symptoms of Parkinson's Disease. The higher levodopa levels also lead to increased levodopa adverse effects, sometimes requiring a decrease in the dose of levodopa.

In animals, while entacapone enters the CNS to a minimal extent, it has been shown to inhibit central COMT activity. In humans, entacapone inhibits the COMT enzyme in peripheral tissues. The effects of entacapone on central COMT activity in humans have not been studied.

Pharmacodynamics: ***COMT Activity in Erythrocytes:*** Studies in healthy volunteers have shown that entacapone reversibly inhibits human erythrocyte catechol-*O*-methyltransferase (COMT) activity after oral administration. There was a linear correlation between entacapone dose and erythrocyte COMT inhibition, the maximum inhibition being 82% following an 800-mg single dose. With a 200-mg single dose of entacapone, maximum inhibition of erythrocyte COMT activity is on average 65% with a return to baseline level within 8 hours.

Effect on the Pharmacokinetics of Levodopa and its Metabolites: When 200 mg entacapone is administered together with levodopa/carbidopa, it increases the area under the curve (AUC) of levodopa by approximately 35% and the elimination half-life of levodopa is prolonged from 1.3 h-2.4 h. In general, the average peak levodopa plasma concentration and the time of its occurrence (T_{max} of 1 hour) are unaffected. The onset of effect occurs after the first administration and is maintained during long-term treatment. Studies in Parkinson's Disease patients suggest that the maximal effect occurs with 200-mg entacapone. Plasma levels of 3-OMD are markedly and dose-dependently decreased by entacapone when given with levodopa/carbidopa.

Pharmacokinetics of Entacapone: Entacapone pharmacokinetics are linear over the dose range of 5 mg-800 mg, and are independent of levodopa/carbidopa coadministration. The elimination of entacapone is biphasic, with an elimination half-life of 0.4 h-0.7 h based on the β-phase and 2.4 h based on the γ-phase. The γ-phase accounts for approximately 10% of the total AUC. The total body clearance after i.v. administration is 850 mL/min. After a single 200-mg dose of Comtan (entacapone), the C_{max} is approximately 1.2 µg/mL.

Absorption: Entacapone is rapidly absorbed, with a T_{max} of approximately 1 hour. The absolute bioavailability following oral administration is 35%. Food does not affect the pharmacokinetics of entacapone.

Distribution: The volume of distribution of entacapone at steady state after i.v. injection is small (20 L). Entacapone does not distribute widely into tissues due to its high plasma protein binding. Based on *in vitro* studies, the plasma protein binding of entacapone is 98% over the concentration range of 0.4-50 µg/mL. Entacapone binds mainly to serum albumin.

Metabolism and Elimination: Entacapone is almost completely metabolized prior to excretion, with only a very small amount (0.2% of dose) found unchanged in urine. The main metabolic pathway is isomerization to the *cis*-isomer, followed by direct glucuronidation of the parent and *cis*-isomer; the glucuronide conjugate is inactive. After oral administration of a ^{14}C-labeled dose of entacapone, 10% of labeled parent and metabolite is excreted in urine and 90% in feces.

Special Populations: Entacapone pharmacokinetics are independent of age. No formal gender studies have been conducted. Racial representation in clinical trials was largely limited to Caucasians (there were only 4 blacks in one US trial and no Asians in any of the clinical trials); no conclusions can therefore be reached about the effect of Comtan on groups other than Caucasian.

Hepatic Impairment: A single 200-mg dose of entacapone, without levodopa/dopa decarboxylase inhibitor coadministration, showed approximately twofold higher AUC and C_{max} values in patients with a history of alcoholism and hepatic impairment (n=10) compared to normal subjects (n=10). All patients had biopsy-proven liver cirrhosis caused by alcohol. According to Child-Pugh grading 7 patients with liver disease had mild hepatic impairment and 3 patients had moderate hepatic impairment. As only about 10% of the entacapone dose is excreted in urine as parent compound and conjugated glucuronide, biliary excretion appears to be the major route of excretion of this drug. Consequently, entacapone should be administered with care to patients with biliary obstruction.

Renal Impairment: The pharmacokinetics of entacapone have been investigated after a single 200-mg entacapone dose, without levodopa/dopa decarboxylase inhibitor coadministration, in a specific renal impairment study. There were three groups: normal subjects (n=7; creatinine clearance >1.12 mL/sec/1.73 m²), moderate impairment (n=10; creatinine clearance ranging from 0.60-0.89 mL/sec/1.73 m²), and severe impairment (n=7; creatinine clearance ranging from 0.20-0.44 mL/sec/1.73 m²). No important effects of renal function on the pharmacokinetics of entacapone were found.

Drug Interactions: *See PRECAUTIONS, Drug Interactions.*

Clinical Studies: The effectiveness of Comtan (entacapone) as an adjunct to levodopa in the treatment of Parkinson's Disease was established in three 24-week multicenter, randomized, double-blind placebo-controlled trials in patients with Parkinson's Disease. In two of these trials, the patients' disease was "fluctuating", i.e., was characterized by documented periods of "On" (periods of relatively good functioning) and "Off" (periods of relatively poor functioning), despite optimum levodopa therapy. There was also a withdrawal period following 6 months of treatment. In the third trial patients were not required to have been experiencing fluctuations. Prior to the controlled part of the trials, patients were stabilized on levodopa for 2-4 weeks. Comtan has not been systematically evaluated in patients who do not experience fluctuations.

In the first two studies to be described, patients were randomized to receive placebo or entacapone 200 mg administered concomitantly with each dose of levodopa/carbidopa (up to 10 times daily, but averaging 4-6 doses per day). The formal double-blind portion of both trials was 6 months long. Patients recorded the time spent in the "On" and "Off" states in home diaries periodically throughout the duration of the trial. In one study, conducted in the Nordic countries, the primary outcome measure was the total mean time spent in the "On" state during an 18-hour diary recorded day (6 AM to midnight). In the other study, the primary outcome measure was the proportion of awake time spent over 24 hours in the "On" state.

In addition to the primary outcome measure, the amount of time spent in the "Off" state was evaluated, and patients were also evaluated by subparts of the Unified Parkinson's Disease Rating Scale (UPDRS), a frequently used multi-item rating scale intended to assess mentation (Part I), activities of daily living (Part II), motor function (Part III), complications of therapy (Part IV), and disease staging (Part V & VI); an investigator's and patient's global assessment of clinical condition, a 7-point subjective scale designed to assess global functioning in Parkinson's Disease; and the change in daily levodopa/carbidopa dose.

In one of the studies, 171 patients were randomized in 16 centers in Finland, Norway, Sweden, and Denmark (Nordic study), all of whom received concomitant levodopa plus dopa-decarboxylase inhibitor (either levodopa/carbidopa or levodopa/benserazide). In the second trial, 205 patients were randomized in 17 centers in North America (US and Canada); all patients received concomitant levodopa/carbidopa.

The following tables display the results of these two trials:

Table 1. Nordic Study

	Baseline	Change from Baseline at Month 6*	p-value vs. placebo
Primary Measure from Home Diary (from an 18-hour Diary Day)			
Hours of Awake Time "On"			
Placebo	9.2	+0.1	–
Comtan	9.3	+1.5	<0.001
Duration of "On" time after first AM dose (hrs)			
Placebo	2.2	0.0	–
Comtan	2.1	+0.2	<0.05
Secondary Measures from Home Diary (from an 18-hour Diary Day)			
Hours of Awake Time "Off"			
Placebo	5.3	0.0	–
Comtan	5.5	-1.3	<0.001
Proportion of Awake Time "On" * (%)**			
Placebo	63.8	+0.6	–
Comtan	62.7	+9.3	<0.001
Levodopa Total Daily Dose (mg)			
Placebo	705	+14	–
Comtan	701	-87	<0.001
Frequency of Levodopa Daily Intakes			
Placebo	6.1	+0.1	–
Comtan	6.2	-0.4	<0.001
Other Secondary Measures			
Investigator's Global (overall) % Improved**			
Placebo	–	28	–
Comtan	–	56	<0.01
Patient's Global (overall) % Improved**			
Placebo	–	22	–
Comtan	–	39	N.S.‡
UPDRS Total			
Placebo	37.4	-1.1	–
Comtan	38.5	-4.8	<0.01
UPDRS Motor			
Placebo	24.6	-0.7	–
Comtan	25.5	-3.3	<0.05
UPDRS ADL			
Placebo	11.0	-0.4	–
Comtan	11.2	-1.8	<0.05

* Mean; the month 6 values represent the average of weeks 8, 16, and 24, by protocol-defined outcome measure.

** At least one category change at endpoint.

*** Not an endpoint for this study but primary endpoint in the North American Study.

‡ Not significant.

Table 2. North American Study

	Baseline	Change from Baseline at Month 6*	p-value vs. placebo
Primary Measure from Home Diary (for a 24-hour Diary Day)			
Percent of Awake Time "On"			
Placebo	60.8	+2.0	–
Comtan	60.0	+6.7	<0.05
Secondary Measures from Home Diary (for a 24-hour Diary Day)			
Hours of Awake Time "Off"			
Placebo	6.6	-0.3	–
Comtan	6.8	-1.2	<0.01
Hours of Awake Time "On"			
Placebo	10.3	+0.4	–
Comtan	10.2	+1.0	N.S.‡
Levodopa Total Daily Dose (mg)			
Placebo	758	+19	–
Comtan	804	-93	<0.001
Frequency of Levodopa Daily Intakes			
Placebo	6.0	+0.2	–
Comtan	6.2	0.0	N.S.‡
Other Secondary Measures			
Investigator's Global (overall) % Improved**			
Placebo	–	21	–
Comtan	–	34	<0.05
Patient's Global (overall) % Improved**			
Placebo	–	20	–
Comtan	–	31	<0.05
UPDRS Total***			
Placebo	35.6	+2.8	–
Comtan	35.1	-0.6	<0.05
UPDRS Motor***			
Placebo	22.6	+1.2	–
Comtan	22.0	-0.9	<0.05
UPDRS ADL***			
Placebo	11.7	+1.1	–
Comtan	11.9	0.0	<0.05

* Mean; the month 6 values represent the average of weeks 8, 16, and 24, by protocol-defined outcome measure.

** At least one category change at endpoint.

*** Score change at endpoint similarly to the Nordic Study.

‡ Not significant.

Effects on "On" time did not differ by age, sex, weight, disease severity at baseline, levodopa dose and concurrent treatment with dopamine agonists or selegiline.

Withdrawal of entacapone: In the North American study, abrupt withdrawal of entacapone, without alteration of the dose of levodopa/carbidopa, resulted in a significant worsening of fluctuations, compared to placebo. In some cases, symptoms were slightly worse than at baseline, but returned to approximately baseline severity within two weeks following levodopa dose increase on average by 80 mg. In the Nordic study, similarly, a significant worsening of parkinsonian symptoms was observed after entacapone withdrawal, as assessed two weeks after drug withdrawal. At this phase, the symptoms were approximately at baseline severity following levodopa dose increase by about 50 mg.

In the third placebo controlled trial, a total of 301 patients were randomized in 32 centers in Germany and Austria. In this trial, as in the other two trials, entacapone 200 mg was administered with each dose of levodopa/dopa decarboxylase inhibitor (up to 10 times daily) and UPDRS Parts II and III and total daily "On" time were the primary measures of effectiveness. The following results were seen for the primary measures, as well as for some secondary measures:

Table 3. German-Austrian Study

	Baseline	Change from Baseline at Month 6	p-value vs. placebo (LOCF)
Primary Measures			
UPDRS ADL*			
Placebo	12.0	+0.5	–
Comtan	12.4	-0.4	<0.05
UPDRS Motor*			
Placebo	24.1	+0.1	–
Comtan	24.9	-2.5	<0.05
Hours of Awake Time "On" (Home diary)**			
Placebo	10.1	+0.5	–
Comtan	10.2	+1.1	N.S.‡
Secondary Measures			
UPDRS Total*			
Placebo	37.7	+0.6	–
Comtan	39.0	-3.4	<0.05
Percent of Awake Time "On" (Home diary)**			
Placebo	59.8	+3.5	–
Comtan	62.0	+6.5	N.S.‡
Hours of Awake Time "Off" (Home diary)**			
Placebo	6.8	-0.6	–
Comtan	6.3	-1.2	0.07
Levodopa Total Daily Dose (mg)*			
Placebo	572	+4	–
Comtan	566	-35	N.S.‡
Frequency of Levodopa Daily Intake*			
Placebo	5.6	+0.2	–
Comtan	5.4	0.0	<0.01
Global (overall) % Improved***			
Placebo	–	34	–
Comtan	–	38	N.S.‡

* Total population; score change at endpoint.

** Fluctuating population, with 5-10 doses; score change at endpoint.

*** Total population; at least one category change at endpoint.

‡ Not significant.

INDICATIONS

Comtan (entacapone) is indicated as an adjunct to levodopa/carbidopa to treat patients with idiopathic Parkinson's Disease who experience the signs and symptoms of end-of-dose "wearing-off" *(see CLINICAL PHARMACOLOGY, Clinical Studies).*

Comtan's effectiveness has not been systematically evaluated in patients with idiopathic Parkinson's Disease who do not experience end-of-dose "wearing-off".

CONTRAINDICATIONS

Comtan (entacapone) tablets are contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients.

WARNINGS

Monoamine oxidase (MAO) and COMT are the two major enzyme systems involved in the metabolism of catecholamines. It is theoretically possible, therefore, that the combination of Comtan (entacapone) and a non-selective MAO inhibitor (e.g., phenelzine and tranylcypromine) would result in inhibition of the majority of the pathways responsible for normal catecholamine metabolism. For this reason, patients should ordinarily not be treated concomitantly with Comtan and a non-selective MAO inhibitor.

Entacapone can be taken concomitantly with a selective MAO-B inhibitor (e.g., selegiline).

Drugs Metabolized by Catechol-*O*-methyltransferase (COMT): When a single 400-mg dose of entacapone was given together with intravenous isoprenaline (isoproterenol) and epinephrine without coadministered levodopa/dopa decarboxylase inhibitor, the overall mean maximal changes in heart rate during infusion were about 50% and 80% higher than with placebo, for isoprenaline and epinephrine, respectively.

Therefore, drugs known to be metabolized by COMT, such as isoproterenol, epinephrine, norepinephrine, dopamine, dobutamine, alpha-methyldopa, apomorphine, isoetherine, and bitolterol should be administered with caution in patients receiving entacapone regardless of the route of administration (including inhalation), as their interaction may result in increased heart rates, possibly arrhythmias, and excessive changes in blood pressure.

Ventricular tachycardia was noted in one 32-year-old healthy male volunteer in an interaction study after epinephrine infusion and oral entacapone administration. Treatment with propranolol was required. A causal relationship to entacapone administration appears probable but cannot be attributed with certainty.

PRECAUTIONS

Hypotension/Syncope: Dopaminergic therapy in Parkinson's Disease patients has been associated with orthostatic hypotension. Entacapone enhances levodopa bioavailability and, therefore, might be expected to increase the occurrence of orthostatic hypotension. In Comtan (entacapone) clinical trials, however, no differences from placebo were seen for measured orthostasis or symptoms of orthostasis. Orthostatic hypotension was documented at least once in 2.7% and 3.0% of the patients treated with 200 mg Comtan and placebo, respectively. A total of 4.3% and 4.0% of the patients treated with 200 mg Comtan and placebo, respectively, reported orthostatic symptoms at some time during their treatment and also had at least one episode of orthostatic hypotension documented (however, the episode of orthostatic symptoms itself was not accompanied by vital sign measurements). Neither baseline treatment with dopamine agonists or selegiline, nor the presence of orthostasis at baseline, increased the risk of orthostatic hypotension in patients treated with Comtan compared to patients on placebo.

In the large controlled trials, approximately 1.2% and 0.8% of 200 mg entacapone and placebo patients, respectively, reported at least one episode of syncope. Reports of syncope were generally more frequent in patients in both treatment groups who had an episode of documented hypotension (although the episodes of syncope, obtained by history, were themselves not documented with vital sign measurement).

Diarrhea: In clinical trials, diarrhea developed in 60 of 603 (10.0%) and 16 of 400 (4.0%) of patients treated with 200 mg Comtan and placebo, respectively. In patients treated with Comtan, diarrhea was generally mild to moderate in severity (8.6%) but was regarded as severe in 1.3%. Diarrhea resulted in withdrawal in 10 of 603 (1.7%) patients, 7 (1.2%) with mild and moderate diarrhea and 3 (0.5%) with severe diarrhea. Diarrhea generally resolved after discontinuation of Comtan. Two patients with diarrhea were hospitalized. Typically, diarrhea presents within 4-12 weeks after entacapone is started, but it may appear as early as the first week and as late as many months after the initiation of treatment.

Hallucinations: Dopaminergic therapy in Parkinson's Disease patients has been associated with hallucinations. In clinical trials, hallucinations developed in approximately 4.0% of patients treated with 200 mg Comtan or placebo. Hallucinations led to drug discontinuation and premature withdrawal from clinical trials in 0.8% and 0% of patients treated with 200 mg Comtan and placebo, respectively. Hallucinations led to hospitalization in 1.0% and 0.3% of patients in the 200 mg Comtan and placebo groups, respectively.

Dyskinesia: Comtan may potentiate the dopaminergic side effects of levodopa and may cause and/or exacerbate preexisting dyskinesia. Although decreasing the dose of levodopa may ameliorate this side effect, many patients in controlled trials continued to experience frequent dyskinesias despite a reduction in their dose of levodopa. The rates of withdrawal for dyskinesia were 1.5% and 0.8% for 200 mg Comtan and placebo, respectively.

Other Events Reported With Dopaminergic Therapy: The events listed below are rare events known to be associated with the use of drugs that increase dopaminergic activity, although they are most often associated with the use of direct dopamine agonists.

Rhabdomyolysis: Cases of severe rhabdomyolysis have been reported with Comtan use. The complicated nature of these cases makes it impossible to determine what role, if any, Comtan played in their pathogenesis. Severe prolonged motor activity including dyskinesia may account for rhabdomyolysis. One case, however, included fever and alteration of consciousness. It is therefore possible that the rhabdomyolysis may be a result of the syndrome described in Hyperpyrexia and Confusion *(see PRECAUTIONS, Other Events Reported With Dopaminergic Therapy).*

Hyperpyrexia and Confusion: Cases of a symptom complex resembling the neuroleptic malignant syndrome characterized by elevated temperature, muscular rigidity, altered consciousness, and elevated CPK have been reported in association with the rapid dose reduction or withdrawal of other dopaminergic drugs. Several cases with similar signs and symptoms have been reported in association with Comtan therapy, although no information about dose manipulation is available. The complicated nature of these cases makes it difficult to determine what role, if any, Comtan may have played in their pathogenesis. No cases have been reported following the abrupt withdrawal or dose reduction of entacapone treatment during clinical studies.

Prescribers should exercise caution when discontinuing entacapone treatment. When considered necessary, withdrawal should proceed slowly. If a decision is made to discontinue treatment with Comtan, recommendations include monitoring the patient closely and adjusting other dopaminergic treatments as needed. This syndrome should be considered in the differential diagnosis for any patient who develops a high fever or severe rigidity. Tapering Comtan has not been systematically evaluated.

Fibrotic Complications: Cases of retroperitoneal fibrosis, pulmonary infiltrates, pleural effusion, and pleural thickening have been reported in some patients treated with ergot derived dopaminergic agents. These complications may resolve when the drug is discontinued, but complete resolution does not always occur. Although these adverse events are believed to be related to the ergoline structure of these compounds, whether other, nonergot derived drugs (e.g., entacapone) that increase dopaminergic activity can cause them is unknown. It should be noted that the expected incidence of fibrotic complications is so low that even if entacapone caused these complications at rates similar to those attributable to other dopaminergic therapies, it is unlikely that it would have been detected in a cohort of the size exposed to entacapone. Four cases of pulmonary fibrosis were reported during clinical development of entacapone; three of these patients were also treated with pergolide and one with bromocriptine. The duration of treatment with entacapone ranged from 7-17 months.

Renal Toxicity: In a 1 year toxicity study, entacapone (plasma exposure 20 times that in humans receiving the maximum recommended daily dose of 1600 mg) caused an increased incidence in male rats of nephrotoxicity that was characterized by regenerative tubules, thickening of basement membranes, infiltration of mononuclear cells and tubular protein casts. These effects were not associated with changes in clinical chemistry parameters, and there is no established method for monitoring for the possible occurrence of these lesions in humans. Although this toxicity could represent a species-specific effect, there is not yet evidence that this is so.

Hepatic Impairment: Patients with hepatic impairment should be treated with caution. The AUC and C_{max} of entacapone approximately doubled in patients with documented liver disease compared to controls. *(See CLINICAL PHARMACOLOGY, Pharmacokinetics of Entacapone and DOSAGE AND ADMINISTRATION).*

Information for Patients: Patients should be instructed to take Comtan only as prescribed.

Patients should be informed that hallucinations can occur.

Patients should be advised that they may develop postural (orthostatic) hypotension with or without symptoms such as dizziness, nausea, syncope, and sweating. Hypotension may occur more frequently during initial therapy. Accordingly, patients should be cautioned against rising rapidly after sitting or lying down, especially if they have been doing so for prolonged periods, and especially at the initiation of treatment with Comtan.

Patients should be advised that they should neither drive a car nor operate other complex machinery until they have gained sufficient experience on Comtan to gauge whether or not it affects their mental and/or motor performance adversely. Because of the possible additive sedative effects, caution should be used when patients are taking other CNS depressants in combination with Comtan.

Patients should be informed that nausea may occur, especially at the initiation of treatment with Comtan.

Patients should be advised of the possibility of an increase in dyskinesia.

Patients should be advised that treatment with entacapone may cause a change in the color of their urine (a brownish orange discoloration) that is not clinically relevant. In controlled trials, 10% of patients treated with Comtan reported urine discoloration compared to 0% of placebo patients.

Although Comtan has not been shown to be teratogenic in animals, it is always given in conjunction with levodopa/carbidopa, which is known to cause visceral and skeletal malformations in the rabbit. Accordingly, patients should be advised to notify their physicians if they become pregnant or intend to become pregnant during therapy *(see PRECAUTIONS, Pregnancy).*

Entacapone is excreted into maternal milk in rats. Because of the possibility that entacapone may be excreted into human maternal milk, patients should be advised to notify their physicians if they intend to breastfeed or are breastfeeding an infant.

Laboratory Tests: Comtan is a chelator of iron. The impact of entacapone on the body's iron stores is unknown; however, a tendency towards decreasing serum iron concentrations was noted in clinical trials. In a controlled clinical study serum ferritin levels (as marker of iron deficiency and subclinical anemia) were not changed with entacapone compared to placebo after one year of treatment and there was no difference in rates of anemia or decreased hemoglobin levels.

Special Populations: Patients with hepatic impairment should be treated with caution *(see INDICATIONS, DOSAGE AND ADMINISTRATION).*

Drug Interactions: *In vitro* studies of human CYP enzymes showed that entacapone inhibited the CYP enzymes 1A2, 2A6, 2C9, 2C19, 2D6, 2E1 and 3A only at very high concentrations (IC50 from 200 to over 1000 µM; an oral 200 mg dose achieves a highest level of approximately 5 µM in people); these enzymes would therefore not be expected to be inhibited in clinical use.

Protein Binding: Entacapone is highly protein bound (98%). *In vitro* studies have shown no binding displacement between entacapone and other highly bound drugs, such as warfarin, salicylic acid, phenylbutazone, and diazepam.

Drugs Metabolized by Catechol-*O*-methyltransferase (COMT): *See WARNINGS.*

Hormone levels: Levodopa is known to depress prolactin secretion and increase growth hormone levels. Treatment with entacapone coadministered with levodopa/dopa decarboxylase inhibitor does not change these effects.

Effect of Entacapone on the Metabolism of Other Drugs: *See WARNINGS* regarding concomitant use of Comtan and non-selective MAO inhibitors.

No interaction was noted with the MAO-B inhibitor selegiline in two multiple-dose interaction studies when entacapone was coadministered with a levodopa/dopa decarboxylase inhibitor (n=29). More than 600 Parkinson's Disease patients in clinical trials have used selegiline in combination with entacapone and levodopa/dopa decarboxylase inhibitor.

As most entacapone excretion is via the bile, caution should be exercised when drugs known to interfere with biliary excretion, glucuronidation, and intestinal beta-glucuronidase are given concurrently with entacapone. These include probenecid, cholestyramine, and some antibiotics (e.g., erythromycin, rifampicin, ampicillin and chloramphenicol).

No interaction with the tricyclic antidepressant imipramine was shown in a single-dose study with entacapone without coadministered levodopa/dopa-decarboxylase inhibitor.

Carcinogenesis: Two-year carcinogenicity studies of entacapone were conducted in mice and rats. Rats were treated once daily by oral gavage with entacapone doses of 20, 90, or 400 mg/kg. An increased incidence of renal tubular adenomas and carcinomas was found in male rats treated with the highest dose of entacapone. Plasma exposures (AUC) associated with this dose were approximately 20 times higher than estimated plasma exposures of humans receiving the maximum recommended daily dose of entacapone (MRDD = 1600 mg). Mice were treated once daily by oral gavage with doses of 20, 100 or 600 mg/kg of entacapone (0.05, 0.3, and 2 times the MRDD for humans on a mg/m² basis). Because of a high incidence of premature mortality in mice receiving the highest dose of entacapone, the mouse study is not an adequate assessment of carcinogenicity. Although no treatment related tumors were observed in animals receiving the lower doses, the carcinogenic potential of entacapone has not been fully evaluated. The carcinogenic potential of entacapone administered in combination with levodopa/carbidopa has not been evaluated.

Mutagenesis: Entacapone was mutagenic and clastogenic in the *in vitro* mouse lymphoma/thymidine kinase assay in the presence and absence of metabolic activation, and was clastogenic in cultured human lymphocytes in the presence of metabolic activation. Entacapone, either alone or in combination with levodopa/carbidopa, was not clastogenic in the *in vivo* mouse micronucleus test or mutagenic in the bacterial reverse mutation assay (Ames test).

Impairment of Fertility: Entacapone did not impair fertility or general reproductive performance in rats treated with up to 700 mg/kg/day (plasma AUCs 28 times those in humans receiving the MRDD). Delayed mating, but no fertility impairment, was evident in female rats treated with 700 mg/kg/day of entacapone.

Pregnancy: ***Pregnancy Category C.*** In embryofetal development studies, entacapone was administered to pregnant animals throughout organogenesis at doses of up to 1000 mg/kg/day in rats and 300 mg/kg/day in rabbits. Increased incidences of fetal variations were evident in litters from rats treated with the highest dose, in the absence of overt signs of maternal toxicity. The maternal plasma drug exposure (AUC) associated with this dose was approximately 34 times the estimated plasma exposure in humans receiving the maximum recommended daily dose (MRDD) of 1600 mg. Increased frequencies of abortions and late/total resorptions and decreased fetal weights were observed in the litters of rabbits treated with maternotoxic doses of 100 mg/kg/day (plasma AUCs 0.4 times those in humans receiving the MRDD) or greater. There was no evidence of teratogenicity in these studies.

However, when entacapone was administered to female rats prior to mating and during early gestation, an increased incidence of fetal eye anomalies (macrophthalmia, microphthalmia, anophthalmia) was observed in the litters of dams treated with doses of 160 mg/kg/day (plasma AUCs 7 times those in humans receiving the MRDD) or greater, in the absence of maternotoxicity. Administration of up to 700 mg/kg/day (plasma AUCs 28 times those in humans receiving the MRDD) to female rats during the latter part of gestation and throughout lactation, produced no evidence of developmental impairment in the offspring.

Entacapone is always given concomitantly with levodopa/carbidopa, which is known to cause visceral and skeletal malformations in rabbits. The teratogenic potential of entacapone in combination with levodopa/carbidopa was not assessed in animals.

There is no experience from clinical studies regarding the use of Comtan in pregnant women. Therefore, Comtan should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Women: In animal studies, entacapone was excreted into maternal rat milk. It is not known whether entacapone is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when entacapone is administered to a nursing woman.

Pediatric Use: There is no identified potential use of entacapone in pediatric patients.

ADVERSE REACTIONS

During the pre-marketing development of entacapone, 1450 patients with Parkinson's Disease were treated with entacapone. Included were patients with fluctuating symptoms, as well as those with stable responses to levodopa therapy. All patients received concomitant treatment with levodopa preparations, however, and were similar in other clinical aspects.

The most commonly observed adverse events (>5%) in the double-blind, placebo-controlled trials (N=1003) associated with the use of Comtan (entacapone) and not seen at an equivalent frequency among the placebo-treated patients were: dyskinesia/hyperkinesia, nausea, urine discoloration, diarrhea, and abdominal pain.

Approximately 14% of the 603 patients given entacapone in the double-blind, placebo-controlled trials discontinued treatment due to adverse events compared to 9% of the 400 patients who received placebo. The most frequent causes of discontinuation in decreasing order are: psychiatric reasons (2% vs. 1%), diarrhea (2% vs. 0%), dyskinesia/hyperkinesia (2% vs. 1%), nausea (2% vs. 1%), abdominal pain (1% vs. 0%), and aggravation of Parkinson's Disease symptoms (1% vs. 1%).

Adverse Event Incidence in Controlled Clinical Studies: Table 4 lists treatment emergent adverse events that occurred in at least 1% of patients treated with entacapone participating in the double-blind, placebo-controlled studies and that were numerically more common in the entacapone group, compared to placebo. In these studies, either entacapone or placebo was added to levodopa/carbidopa (or levodopa/benserazide).

Table 4
Summary of Patients with Adverse Events after Start of Trial Drug Administration
At least 1% in Comtan® (entacapone) group and > Placebo

SYSTEM ORGAN CLASS Preferred term	Comtan (n = 603) % of patients	Placebo (n = 400) % of patients
SKIN AND APPENDAGES DISORDERS		
Sweating increased	2	1
MUSCULOSKELETAL SYSTEM DISORDERS		
Back pain	2	1
CENTRAL & PERIPHERAL NERVOUS SYSTEM DISORDERS		
Dyskinesia	25	15
Hyperkinesia	10	5
Hypokinesia	9	8
Dizziness	8	6
SPECIAL SENSES, OTHER DISORDERS		
Taste perversion	1	0
PSYCHIATRIC DISORDERS		
Anxiety	2	1
Somnolence	2	0
Agitation	1	0
GASTROINTESTINAL SYSTEM DISORDERS		
Nausea	14	8
Diarrhea	10	4
Abdominal pain	8	4
Constipation	6	4
Vomiting	4	1
Mouth dry	3	0
Dyspepsia	2	1
Flatulence	2	0
Gastritis	1	0
Gastrointestinal disorders nos	1	0
RESPIRATORY SYSTEM DISORDERS		
Dyspnea	3	1
PLATELET, BLEEDING & CLOTTING DISORDERS		
Purpura	2	1
URINARY SYSTEM DISORDERS		
Urine discoloration	10	0
BODY AS A WHOLE - GENERAL DISORDERS		
Back pain	4	2
Fatigue	6	5
Asthenia	2	1
RESISTANCE MECHANISM DISORDERS		
Infection bacterial	1	0

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical studies. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures do, however, provide the prescriber with some basis for estimating the relative contribution of drug and nondrug factors to the adverse events observed in the population studied.

Effects of gender and age on adverse reactions: No differences were noted in the rate of adverse events attributable to entacapone by age or gender.

DRUG ABUSE AND DEPENDENCE

Comtan (entacapone) is not a controlled substance. Animal studies to evaluate the drug abuse and potential dependence have not been conducted. Although clinical trials have not revealed any evidence of the potential for abuse, tolerance or physical dependence, systematic studies in humans designed to evaluate these effects have not been performed.

OVERDOSAGE

There have been no reported cases of either accidental or intentional overdose with entacapone tablets. However, COMT inhibition by entacapone treatment is dose-dependent. A massive overdose of Comtan (entacapone) may theoretically produce a 100% inhibition of the COMT enzyme in people, thereby preventing the metabolism of endogenous and exogenous catechols.

The highest single dose of entacapone administered to humans was 800 mg, resulting in a plasma concentration of 14.1 µg/mL. The highest daily dose given to humans was 2400 mg, administered in one study as 400 mg six times daily with levodopa/carbidopa for 14 days in 15 Parkinson's Disease patients, and in another study as 800 mg t.i.d. for 7 days in 8 healthy volunteers. At this daily dose, the peak plasma concentrations of entacapone averaged 2.0 µg/mL (at 45 min., compared to 1.0 and 1.2 µg/mL with 200 mg entacapone at 45 min.). Abdominal pain and loose stools were the most commonly observed adverse events during this study. Daily doses as high as 2000 mg Comtan have been administered as 200 mg 10 times daily with levodopa/carbidopa or levodopa/benserazide for at least 1 year in 10 patients, for at least 2 years in 8 patients and for at least 3 years in 7 patients. Overall, however, clinical experience with daily doses above 1600 mg is limited.

The range of lethal plasma concentrations of entacapone based on animal data was 80-130 µg/mL in mice. Respiratory difficulties, ataxia, hypoactivity, and convulsions were observed in mice after high oral (gavage) doses.

Management of Overdose: Management of Comtan overdose is symptomatic; there is no known antidote to Comtan. Hospitalization is advised, and general supportive care is indicated. There is no experience with hemodialysis or hemoperfusion, but these procedures are unlikely to be of benefit, because Comtan is highly bound to plasma proteins. An immediate gastric lavage and repeated doses of charcoal over time may hasten the elimination of Comtan by decreasing its absorption/reabsorption from the GI tract. The adequacy of the respiratory and circulatory systems should be carefully monitored and appropriate supportive measures employed. The possibility of drug interactions, especially with catechol-structured drugs, should be borne in mind.

DOSAGE AND ADMINISTRATION

The recommended dose of Comtan (entacapone) is one 200 mg tablet administered concomitantly with each levodopa/carbidopa dose to a maximum of 8 times daily (200 mg x 8 = 1600 mg per day). Clinical experience with daily doses above 1600 mg is limited.

Comtan should always be administered in association with levodopa/carbidopa. Entacapone has no antiparkinsonian effect of its own.

In clinical trials, the majority of patients required a decrease in daily levodopa dose if their daily dose of levodopa had been ≥800 mg or if patients had moderate or severe dyskinesias before beginning treatment.

To optimize an individual patient's response, reductions in daily levodopa dose or extending the interval between doses may be necessary. In clinical trials, the average reduction in daily levodopa dose was about 25% in those patients requiring a levodopa dose reduction. (More than 58% of patients with levodopa doses above 800 mg daily required such a reduction.)

Comtan can be combined with both the immediate and sustained-release formulations of levodopa/carbidopa.

Comtan may be taken with or without food *(see CLINICAL PHARMACOLOGY).*

Patients With Impaired Hepatic Function: Patients with hepatic impairment should be treated with caution. The AUC and C_{max} of entacapone approximately doubled in patients with documented liver disease, compared to controls. However, these studies were conducted with single-dose entacapone without levodopa/dopa decarboxylase inhibitor coadministration, and therefore the effects of liver disease on the kinetics of chronically administered entacapone have not been evaluated *(see CLINICAL PHARMACOLOGY, Pharmacokinetics of Entacapone).*

Withdrawing Patients from Comtan: Rapid withdrawal or abrupt reduction in the Comtan dose could lead to emergence of signs and symptoms of Parkinson's Disease *(see CLINICAL PHARMACOLOGY, Clinical Studies),* and may lead to Hyperpyrexia and Confusion, a symptom complex resembling the neuroleptic malignant syndrome *(see PRECAUTIONS, Other Events Reported With Dopaminergic Therapy).* This syndrome should be considered in the differential diagnosis for any patient who develops a high fever or severe rigidity. If a decision is made to discontinue treatment with Comtan, patients should be monitored closely and other dopaminergic treatments should be adjusted as needed. Although tapering Comtan has not been systematically evaluated, it seems prudent to withdraw patients slowly if the decision to discontinue treatment is made.

HOW SUPPLIED

Comtan (entacapone) is supplied as 200-mg film-coated tablets for oral administration. The oval-shaped tablets are brownish-orange, unscored, and embossed "COMTAN" on one side. Tablets are provided in HDPE containers as follows:

Bottles of 100 ..... NDC 0078-0327-05

Store at 25°C (77°F) excursions permitted to 15°-30°C (59°-86°F).
[See USP Controlled Room Temperature.]

Comtan (entacapone) tablets are manufactured by Orion Corporation, Orion Pharma (Espoo, Finland) and marketed by Novartis Pharmaceuticals Corporation (East Hanover, N.J. 07936, U.S.A.).

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