How did Creutzfeldt-Jakob disease (CJD) occur in people treated with pituitary human growth hormone (hGH)?

Before scientists learned how to make synthetic hormones, many animal hormones, such as insulin, were used to treat human disorders. Growth hormone from animals did not work in humans. Human growth hormone (pituitary hGH) was therefore made from human pituitary glands by the National Hormone and Pituitary Program (NHPP), funded by the U.S. Department of Health and Human Services (HHS). From 1963 to 1985, the NHPP sent pituitary hGH to hundreds of doctors across the country. As a part of research studies, doctors used the hormone to treat nearly 7,700 children for failure to grow.

In 1985, the HHS learned that three young men treated with pituitary hGH died of Creutzfeldt-Jakob disease (CJD), a rare and incurable brain disease. The HHS believed these illnesses were related to pituitary hGH. The HHS immediately stopped the distribution of the hormone and began a national study to learn more about how pituitary hGH treatment may have caused this problem. The HHS continues to monitor individuals who received pituitary hGH through the NHPP for CJD.

How many people treated with NHPP-distributed hGH got CJD in the United States?

The HHS has identified 29 cases of CJD among the nearly 7,700 people in the United States who received NHPP pituitary hGH. None of the 29 people who got CJD began treatment with pituitary hGH after 1977, the year that the NHPP began producing pituitary hGH in a laboratory (headed by Dr. Albert Parlow) using a new purification step. Today, the growth hormone used to treat patients is made biosynthetically and not from human pituitary glands. Biosynthetic growth hormone (bGH), also known as recombinant human growth hormone (rhGH), poses no threat of infection with CJD.
Based on NHPP records, the HHS estimated 7,700 people were treated with pituitary hGH from the NHPP. Of these, the HHS got the names and addresses of 6,272 from their doctors and treatment centers so that their health could be monitored. Another 1,400 people are believed to have been treated with pituitary hGH; however, the HHS does not have their names and addresses. The HHS hoped to learn about CJD and other health problems in the unmonitored group of 1,400 and notified many doctors about the problem of CJD, asking them to report CJD among people treated with pituitary hGH. The HHS has learned that five of the 29 people with confirmed CJD were among the 1,400 people the HHS was not able to identify and study.

Some U.S. laboratories that made pituitary hGH for the NHPP also made hGH for use in other countries. The HHS learned that six people in New Zealand and two people in Brazil who received U.S.-made pituitary hGH may also have gotten CJD. A total of 37 people who were treated with pituitary hGH made in the United States may have gotten CJD.

Before bGH was available, several pharmaceutical companies made pituitary hGH. Some children treated in the U.S. received hormone produced by these companies when NHPP hGH was not available to them. Some of the 29 people with confirmed CJD received hGH from both the NHPP and a pharmaceutical company. Recently, the HHS has learned of an individual treated in the U.S. who developed CJD and received only commercial pituitary hGH. That person was not eligible for NHPP hGH and received pituitary hGH made by two pharmaceutical companies.

**How many people treated with pituitary hGH got CJD in other countries?**

People treated with pituitary hGH in other countries also got CJD. HHS doctors share information with doctors around the world about health issues such as CJD and read reports about CJD and other health problems related to pituitary hGH treatment.
<table>
<thead>
<tr>
<th>Country</th>
<th>Number of CJD Cases Reported*</th>
<th>Number of Individuals Treated</th>
<th>Source of hGH in Reported Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Zealand***</td>
<td>6</td>
<td>159</td>
<td>United States</td>
</tr>
<tr>
<td>France</td>
<td>119</td>
<td>1,700</td>
<td>France</td>
</tr>
<tr>
<td>United Kingdom</td>
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<td>United States</td>
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<tr>
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<tr>
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</tr>
<tr>
<td>Ireland</td>
<td>1</td>
<td>unpublished</td>
<td>Not known</td>
</tr>
</tbody>
</table>

*as of November 2014

**This case has been recognized by the Australian surveillance authorities as a “possible” (albeit unlikely) CJD case.

***New Zealand has reported six people with CJD among 159 who received pituitary hGH. All six were among 49 people who received pituitary hGH made by the U.S. lab that supplied most NHPP pituitary hGH before 1977. We don’t know why this rate—six out of 49 (12.2 percent)—is so high in those in New Zealand who received American hormone. HHS scientists believe that this U.S.-made hormone did not undergo the same filtering process used in the United States when the hormone was put into vials. In addition, some hormone preparations sent to New Zealand were not distributed in the United States.
New Zealand has little information on the hormone preparations used to treat the people who got CJD. Information provided to the HHS from medical authorities in New Zealand indicated the following dates of pituitary hGH treatment for the six New Zealand patients who developed CJD: 1964 to 1966, 1964 to 1970, 1965 to 1972, 1966 to 1972, 1967 to 1969, and 1970 to 1973. With no common period of treatment, it is unlikely that a single preparation exposed all six patients to CJD.

There is some information on the hormone sent to New Zealand from the lab that also produced hormone for the NHPP before 1977. Some preparations and components of preparations were used in both countries and others were distributed only in the United States or in New Zealand.

The time between the start of pituitary hGH treatment and the first sign of CJD symptoms was similar in the 29 United States patients (14 to 44 years) and the six New Zealand patients (17 to 37 years). The New Zealand patients who got CJD were treated with pituitary hGH for an average of 4.3 years. In the United States, average treatment time was 8.4 years in patients who got CJD.

In France, 119 people with CJD were among the 1,700 treated with pituitary hGH. The pattern of exposure to CJD in France is very different from the pattern in the United States. In France, people who received pituitary hGH in 1984 and 1985 appear to be at highest risk for CJD. We have learned from animal studies that when scientists injected a greater amount of CJD infectious agent into an animal, it took less time for CJD to develop. Because of the larger number of people with CJD and shorter times between treatment and CJD onset in France, the level of infection in French hormone was probably higher than in the U.S. hormone. The purification procedure used in France differed from that begun in 1977 in the United States.

The United Kingdom has reported 75 people with CJD among 1,849 who received pituitary hGH. Experts have also found CJD in two people in Holland, two people in Brazil, and one each in Australia, Austria, Qatar, and Ireland. France, the United Kingdom, Holland, and Australia made their own hormone. The Brazilian patients got pituitary hGH from a U.S. lab that also made NHPP hormone before 1977. This was a different lab than the U.S. lab that made hormone for New Zealand. The Qatar patient received pituitary hGH made in France. The Austrian patient received pituitary hGH made by a pharmaceutical company. Four Australian women developed CJD after receiving other human pituitary hormones as fertility treatments.

**Are people treated with pituitary hGH at risk for other diseases or problems?**

Most people were treated with pituitary hGH because their pituitary glands did not make enough of their own GH. Some of these people also had problems making other pituitary hormones. One of these hormones tells the adrenal glands to make cortisol, a hormone needed for life. People lacking this hormone are at risk of death from adrenal crisis, but adrenal crisis can be prevented. More pituitary hGH recipients have died from adrenal crisis than from CJD. Pituitary hGH did not cause adrenal problems, but
some people who received hGH have a pituitary problem that puts them at risk for adrenal crisis. Please read the health alert at www.endocrine.niddk.nih.gov/pubs/creutz/alert.aspx and discuss this information with your doctor.

Besides CJD, no other serious or fatal health risks from pituitary hGH treatment have been found.

“Mad Cow” Disease
Starting in 1996, reports of a new form of CJD in young people who lived in the United Kingdom have raised concerns worldwide.

Since at least 1985, some cattle in the United Kingdom have developed a disease called bovine spongiform encephalopathy (BSE), or “mad cow” disease. “Mad cow” disease is a sickness in cattle that is caused by an agent that is similar, but not identical, to the agents that cause the most common forms of CJD in people. Individuals who consume products made from cattle infected with the agent that causes “mad cow” disease can become infected with the agent themselves and develop the human form of “mad cow” disease, called variant CJD (vCJD). In humans, vCJD and the more common forms of CJD (those without the word “variant”) are separate diseases. As of November 2012, 227 cases of vCJD were confirmed worldwide, mostly from the United Kingdom. Researchers believe all but three of these 227 individuals got vCJD by eating beef from animals with “mad cow” disease. The three exceptions were persons who are believed to have developed vCJD because they received infected blood from a donor who had acquired the agent by eating beef from animals with “mad cow” disease.

In the United States, three cases of vCJD have been found. According to the Centers for Disease Control and Prevention (CDC), the investigation of these three cases indicated that they most likely acquired their infection in the United Kingdom (two cases) and Saudi Arabia (one case).

People who received pituitary hGH are not at higher risk for vCJD.

AIDS
HIV, also known as the human immunodeficiency virus, causes AIDS. Pituitary hGH does not cause AIDS. HIV is destroyed by the methods used to make pituitary hGH. People who have been treated with pituitary hGH do not have a higher risk for AIDS.

Low Levels of GH in Adults
Some people who received pituitary hGH as children may have low levels of GH as adults and might therefore benefit from bGH as adults. People with low levels of growth hormone as adults may have symptoms or changes like these:

- more body fat
- less muscle
- less bone mass
- less strength
- less energy

If you lacked GH as a child and have these problems as an adult, ask your doctor whether they might be due to low GH. Because these conditions are common in many people, they are not always due to low GH. Studies have shown that GH treatment in adults with low GH reduces fat and increases muscle mass. Effects on strength, energy, and bone fractures in GH-deficient adults receiving GH replacement are not as clear.
Today, GH is completely synthetic. It is not made from human pituitaries. It poses no threat of contamination. The Human Growth Foundation (HGF) is one source of information about growth-related disorders. The Foundation can be reached at 1–800–451–6434.

Cancer

HHS studies of people treated with pituitary hGH supplied by the NHPP show no increased risk of cancer in those who did not have tumors before pituitary hGH treatment. Many people who received NHPP pituitary hGH had brain tumors that caused their lack of GH. People who have had one tumor have an increased risk for getting other tumors.

In previous updates, we reported that in 1988, Japanese doctors reported an increased risk of leukemia in people treated with GH. Subsequent studies of individuals who were given pituitary hGH in the United States, Japan, and the United Kingdom found no higher rate of leukemia among those who did not have tumors and/or radiation before treatment with pituitary hGH.

Emotional Problems

No studies have shown that pituitary hGH causes changes in personality, emotional problems, or suicide.

What are the symptoms of CJD?

CJD does not cause the same symptoms in everyone. In most people who got CJD from pituitary hGH, the first signs they noticed were difficulty with walking and balance, dizziness, and/or clumsiness. Later, some began to slur words and have jerky movements. They also had trouble seeing, remembering, and/or thinking clearly. The disease becomes worse very quickly. When individuals have symptoms like these over a long period of time (such as a year) without getting much worse, they do not have CJD. Occasional forgetfulness, clumsiness, or headaches do not mean one has CJD. You should discuss concerns with your doctor if you are not sure.

CJD is a rare disease. Most cases of CJD are not linked to pituitary hGH. When CJD is not linked to pituitary hGH, the first symptoms are usually mental changes such as confusion, problems thinking clearly, memory loss, behavior changes, and dementia. Though symptoms may differ, there are similar changes in the brain tissue of all patients with CJD.

What is my risk for getting CJD from NHPP pituitary hGH?

No one can say what an individual person’s risk is. Of the approximately 7,700 people who received NHPP pituitary hGH, 29 people got CJD. The two things that seem to be connected with getting CJD after pituitary hGH treatment are

1. How long a person was treated:
   • In the United States, the average length of time for pituitary hGH treatment through the NHPP was about 3 years. For those individuals who developed CJD, the average length of treatment was about 8.4 years.
   • Even though longer treatment time increased the risk for CJD in the United States, in other countries CJD has developed after shorter treatment periods.
2. When a person was treated:

- All of the 29 individuals treated with NHPP hGH who got CJD in the United States started pituitary hGH before 1977. No CJD has been reported in Americans who began treatment with NHPP hormone after 1977, when production of NHPP hormone was moved to a laboratory (headed by Dr. Albert Parlow) that used a new method of purifying pituitary hGH. Research in animals showed the newer purification steps introduced in 1977 reduced the risk of CJD transmission. Recently, an analysis of NHPP hGH recipients was completed taking into account the differences in follow-up time and the duration of treatment of recipients starting treatment before or after 1977. That analysis found that the new purification steps greatly reduced and may have eliminated the risk for CJD infection.

- Two cases of CJD have been reported in individuals who received commercially prepared pituitary hGH. An Austrian person was treated with pituitary hGH (Crescormon, from Kabi Pharma) for 14 months and died from CJD 22 years later. An American who was too tall to be eligible for NHPP hormone was treated with pituitary hGH made by two pharmaceutical companies (Asellacrin, from Serono, and Crescormon, from Kabi Pharma). This individual was treated with commercial hGH for 23 months and died just over 26 years later. The methods used to produce these commercial hormone preparations were not identical to the method used in Dr. Parlow’s laboratory but did include a version of the important new purification step that has been shown to reduce CJD infectivity.

- Overall, one out of about 265 people (29 out of about 7,700 people) who were treated with NHPP pituitary hGH got CJD.

- However, one in about 91 people who began treatment before 1977 got CJD.

- People who started treatment before 1970 are at even higher risk. In that early group, one in about every 48 people (about 2.1 percent) got CJD.

- The appearance of new cases is decreasing, as there has only been one new case in the past 5 years.

Who can tell me when I was treated and for how long?

The best source for details on your treatment is the doctor or center that gave you pituitary hGH. To protect patient privacy, the HHS did not ask for the names of those treated with pituitary hGH until 1985, when the first CJD cases were reported. In 1985, the HHS asked doctors and treatment centers for the names and addresses of recipients to inform them of the risk of CJD.

We know which pituitary hGH preparations were sent to each treatment center and when they were sent. However, because individual doctors administered the pituitary hGH, we don’t know which preparation each patient might have gotten. We have tried to find this information in the medical records of patients who developed CJD, but many doctors did not note the specific preparation in their records. When records were incomplete, it was assumed that patients who got CJD might have been exposed to all preparations sent to their treatment center during the time they were treated. Since it is impossible to confidently identify high-risk or risk-free hormone, we do not think that details on the hormone preparations that individuals received will help to clarify individual level of risk.
Did the hormone I took cause CJD?

We have not found any particular preparation of pituitary hGH that is especially likely to carry CJD. We believe that CJD did not come from a single infected pituitary gland or preparation. Prior to 1977, in an effort to extract as much hormone as possible from the pituitary glands, the glands were often processed repeatedly. Hormone extracted from the same pituitaries was often included in many hormone preparations. Also, patients who got CJD were treated on average for 8.4 years and received many different hormone preparations. This makes it very difficult to identify any preparation associated with transmitting CJD.

Doctors wanted to see if a specific preparation of pituitary hGH could transmit CJD. To try to find the pituitary hGH that could have caused CJD, HHS researchers did two things:

1. **They set up a test in animals**, injecting samples of all available preparations of pituitary hGH directly into the brains of monkeys. CJD develops more rapidly if injected into the brain than under the skin, as hGH was used in people. The animals were watched for 10 years. The brains of all animals were examined for signs of CJD. If an animal got sick with CJD, it would help researchers to understand which vials of pituitary hGH were contaminated with the agent that causes CJD.

2. **They studied people treated with pituitary hGH** to see who got CJD and which hormone preparation they might have received based on which preparations were sent to their doctor.

Results:

- The animal tests did not help find the pituitary hGH that might have caused CJD. One animal developed the disease 5½ years after injection of pituitary hGH. Two other animals that received injections from different vials of the same pituitary hGH preparation did not develop CJD.

- None of the people who developed CJD are known to have received the hormone preparation that made the animal sick. At most, two patients (whose records are incomplete) may have received this pituitary hGH preparation. Because of this, we do not believe that the patients who received the hormone preparation that transmitted CJD to the animal have a greater risk of developing CJD than others treated with pituitary hGH. Because each preparation of pituitary hGH was used to fill multiple vials, it is not known if CJD contamination was spread evenly among all vials of pituitary hGH that came from a particular preparation. It’s possible that one vial got more contamination and another got little or none from the same preparation of pituitary hGH. It is believed that multiple preparations of pituitary hGH probably had very low levels of the CJD infectious agent. With such low levels of contamination, some vials of a preparation might carry CJD while other vials would not. Further, most of the people who got CJD received pituitary hGH for long periods of time and received many different preparations.
If I develop CJD, will my family get it? If I get pregnant, will my baby get it?

Scientists do not believe that CJD is transmitted through casual day-to-day contact or through sexual contact. Therefore, spouses and children of individuals with CJD are not in danger. Except for rare genetic forms of CJD (which are unrelated to pituitary hGH), a pregnant woman does not pass CJD to her unborn baby. CJD from pituitary hGH does not affect the genes.

Can a test tell if I will get CJD?

Today, when a person has symptoms and findings on neurological examination that may be due to CJD, additional testing may be recommended to help in the diagnosis. Two commonly used tests are the electroencephalogram (EEG) and magnetic resonance imaging (MRI). While these brain tests are useful if they show characteristic features of CJD, such features may be absent, particularly early in the course of the disease. A third test that can help doctors diagnose CJD requires a sample of spinal fluid. To obtain the sample for testing, a doctor performs a lumbar puncture, or spinal tap. A lumbar puncture is considered an invasive test, as a needle is inserted into a person’s spinal canal in the lower back.

Scientists are working on tests to diagnose CJD that are more accurate, safer, and less invasive than the currently available tests. One such test is an easy-to-use nasal brush test that collects cells along the mucous membranes in a person’s nasal cavity for analysis. Although more study is needed before this test can be used on people with neurologic problems, scientists believe the nasal brush test could make it possible to rapidly and accurately diagnose CJD. More information about this new test can be found at www.nih.gov/news/health/aug2014/niaid-06.htm.

Why can’t I donate blood or organs?

Five cases of transmission of the agent that causes vCJD through blood have been reported. vCJD is the disease that occurs in people who ate tainted beef or were exposed to products from cattle with “mad cow” disease. vCJD is different from the classic type of CJD that occurs in pituitary hGH recipients. vCJD is a different disease from CJD. Scientists do not believe that the type of CJD that occurs in GH recipients can be transmitted by blood, but more study is needed. Because no test can rule out the presence of CJD in blood or organs, pituitary hGH recipients are not allowed to donate blood or organs.

Until more is known, the following people should not donate blood or organs:

- Anyone who was treated with pituitary hGH.
- Relatives of individuals with rare genetic forms of CJD; they could harbor CJD even if they do not have symptoms.
- Anyone who has lived in the United Kingdom for 3 months between 1980 and 1996 or in France for 5 years between 1980 and the present.*

People who have been treated only with biosynthetic GH (bGH), in use since 1985, can donate blood and organs. Also, family members of people treated with pituitary hGH can donate blood and organs.

*The U.S. Food and Drug Administration has set these guidelines on blood donation: www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/BloodDonorScreening/UCM164191.pdf.
How is CJD diagnosed?
CJD is usually diagnosed based on signs and symptoms of the illness, how severe they are, and how quickly they become worse. However, doctors must study brain tissue from a biopsy or autopsy in order to make a definite diagnosis of CJD.

Other tests can suggest CJD. In 1996, researchers developed a test that helps doctors diagnose CJD in patients with symptoms. This test detects an abnormal protein in a sample of spinal fluid. When this protein is found, it helps make a diagnosis of CJD. It is much easier and safer to take a sample of spinal fluid than to do a brain biopsy. Unfortunately, this test cannot identify CJD in patients who do not have symptoms. The test cannot predict who may develop CJD in the future.

Researchers from many countries, including the United States, have reported success using MRI to diagnose CJD and vCJD in people with symptoms of the disease. MRI is a safe and painless tool that allows doctors to look at images of the brain and does not involve the collection of brain or spinal fluid samples.

What does research tell us about CJD?
Although CJD is a rare disorder, some of the world’s leading researchers are working hard to learn more about this disease.

About 10 percent of the people who get CJD have the inherited type. Some people have gotten CJD from medical procedures such as pituitary hGH injections, tissue grafts, or corneal transplants. Scientists don’t fully understand what causes CJD. Evidence suggests that a unique infectious agent called a prion [PREE-on] may be the cause. A prion is an unusual infectious agent because it contains no genetic material. It is a protein that takes on different forms. In its normal, harmless form, the protein is curled into a spiral. In its infectious form, the protein folds into an abnormal shape. Somehow, these abnormal proteins change the shape of normal proteins. This change begins a serious chain reaction that results in brain problems.

People with inherited CJD have an abnormal gene that leads to changes in their prion protein. This gene makes the protein likely to assume the abnormal shape. Exposure to the abnormal form of the protein can also occur through injection of contaminated pituitary hGH, tissue grafts, and corneal transplants and through exposures to infected brain tissue.

If CJD results from a defect in protein folding, it may be possible to identify drugs that can help the prion protein assume its proper shape. Such drugs would slow or stop the progress of the disease. Treatments like these are being studied by researchers. Researchers in both Europe and the United States are also trying to develop a test that will identify CJD before symptoms appear.


Why should people treated with pituitary hGH know about CJD?
Some parents did not tell their children about receiving treatment with pituitary hGH and the possible risk of CJD. These children are now adults. Although the HHS no longer sends annual information about the problem of CJD in pituitary hGH recipients, the HHS does maintain a mailing
list should any important new information become available. If parents are no longer available to receive HHS mailings, their adult children may not have access to important new information. Some pituitary hGH recipients have learned about the risk of CJD from newspaper stories. Others heard about it when they tried to give blood. Those who were not told by their parents are often angry when they hear about it outside the family. Any parent of an individual who received pituitary hGH who has not received any mailings from the HHS—the last correspondence was sent in June 1999—should contact the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) with the adult child’s current address. Knowledgeable staff members are glad to answer any questions that parents or recipients may have.

How can the U.S. Department of Health and Human Services (HHS) help me?

If you have any questions, please call the phone numbers listed below. If you call the toll-free number, a recording will ask you to leave your name, phone number, and a good time to reach you. A staff member will call you back. You can also call, write, or have your doctor contact the National Institutes of Health (NIH) at

National Institutes of Health
NIDDK Office of Communications and Public Liaison
Building 31, Room 9A06
31 Center Drive, MSC 2560
Bethesda, MD  20892–2560
Phone:  301–496–3583
Toll-free:  1–800–472–0424
Email:  NIDDK.Inquiries@nih.gov

The website www.endocrine.niddk.nih.gov provides additional information about hGH and CJD. The website is updated when we get new information. We will mail updates in the future only when there is major new information. Some examples would be

- Development of a licensed diagnostic test for non-symptomatic CJD
- Development of preventive therapy or treatment for CJD

We will continue to post information about new reports of CJD and other new information to our website.

How can I get support and information?

The Creutzfeldt-Jakob Disease Foundation, Inc. (www.cjdfoundation.org) was created in 1993 by two families who lost relatives to CJD and the neurologist who treated their family members. This nonprofit corporation seeks to promote awareness of CJD through research and education and to reach out to people who have lost loved ones to this illness. For information on CJD from the NIH, see www.ninds.nih.gov.

The Human Growth Foundation (HGF) (www.hgfound.org) is a nonprofit organization concerned with children’s growth disorders and adult GH deficiency. The HGF has information available online and through its toll-free number, 1–800–451–6434. The HGF also supports an Internet mailing list to help the exchange of information about adult GH deficiency and adult GH replacement therapy.
How can I help with the follow-up study?

Pituitary hGH recipients, their families, and their doctors can help by telling the HHS (NIDDK) of any deaths from any cause in someone who received pituitary hGH, especially if CJD is suspected or confirmed. Family members are asked to give HHS doctors permission to review medical records if a pituitary hGH recipient dies. Allowing the HHS to review these records adds to a growing knowledge base that may benefit thousands of people.

Address changes for pituitary hGH recipients should be sent by recipients, their families, or their doctors to the NIDDK Office of Communications and Public Liaison at the NIH.

Acknowledgments

Publications produced by the Clearinghouse are carefully reviewed by both NIDDK scientists and outside experts.

You may also find additional information about this topic by visiting MedlinePlus at www.medlineplus.gov.

This publication may contain information about medications and, when taken as prescribed, the conditions they treat. When prepared, this publication included the most current information available. For updates or for questions about any medications, contact the U.S. Food and Drug Administration toll-free at 1–888–INFO–FDA (1–888–463–6332) or visit www.fda.gov. Consult your health care provider for more information.

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