Introduction

When protein is eaten, the body breaks it down into amino acids, which help carry out bodily functions. Whatever is not needed by the body is then broken down by the liver and turned into waste products that are cleared out of the body through urine. One of these waste products is ammonia. Too much ammonia in the body is toxic. The liver changes ammonia into a non-toxic substance called urea using a series of specific protein molecules (enzymes). This process is called the urea cycle. Urea cycle disorders are inherited and occur when the body can’t make one or more of the enzymes it needs to turn ammonia into urea. Ammonia builds up in the body and can lead to brain damage, coma, and even death. Urea cycle disorders most often affect infants, though they can affect children and adults. Treatment of urea cycle disorders is meant to reduce the amount of ammonia in the blood to safe levels. This policy describes when drugs used to treat urea cycle disorders may be considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Medical Necessity</th>
</tr>
</thead>
</table>
| **Generic sodium phenylbutyrate**        | **Generic sodium phenylbutyrate may be considered medically necessary when the following criteria are met:**  
• Generic sodium phenylbutyrate is used as adjunctive therapy for the chronic management of patients with urea cycle disorders  
**AND**  
• Documented by genetic testing deficiencies of carbamylphosphate synthetase (CPS), ornithine transcarbamylase (OTC), or argininosuccinic acid synthetase (AS)  
**AND**  
• Documented dietary protein restriction plan is in place |
| Urea Cycle Pathway Alternative            |                                                                                                                                                  |
| **Buphenyl® (sodium phenylbutyrate)**    | **Buphenyl® (sodium phenylbutyrate) may be considered medically necessary when the following criteria are met:**  
• Buphenyl® is used as adjunctive therapy for the chronic management of patients with urea cycle disorders  
**AND**  
• Patient has tried generic sodium phenylbutyrate first and has an inadequate response or intolerance to generic sodium phenylbutyrate (documentation required)  
**AND**  
• Documented by genetic testing deficiencies of carbamylphosphate synthetase (CPS), ornithine transcarbamylase (OTC), or argininosuccinic acid synthetase (AS)  
**AND**  
• Documented dietary protein restriction plan is in place |
| Urea Cycle Pathway Alternative            |                                                                                                                                                  |
| **Carbaglu® (carglumic acid)**           | **Carbaglu® (carglumic acid) may be considered medically necessary when the following criteria are met:**  
• Carbaglu® is used for the treatment of acute or chronic hyperammonemia  
**AND**  
• Documented by genetic testing deficiency of the hepatic enzyme N-acetylglutamate synthase (NAGS) |
| Carbamoyl Phosphate Synthetase 1 Activator|                                                                                                                                                  |
| **Ravicti™ (glycerol phenylbutyrate)**   | **Ravicti™ (glycerol phenylbutyrate) may be considered medically necessary when the following criteria are met:**  
• Ravicti™ is used as adjunctive therapy for the chronic |
|                                           |                                                                                                                                                  |
Drug | Medical Necessity
--- | ---
Nitrogen Binding Agent | management of patients with urea cycle disorders AND • Documented dietary protein restriction plan is in place AND • Patient has tried and failed Buphenyl® (sodium phenylbutyrate) unless there is a contraindication to use of Buphenyl®

Drug | Investigational
--- | ---
Generic sodium phenylbutyrate, Buphenyl® (sodium phenylbutyrate), Carbaglu® (carglumic acid), Ravicti™ (glycerol phenylbutyrate) | All other uses of generic sodium phenylbutyrate, Buphenyl® (sodium phenylbutyrate), Carbaglu® (carglumic acid), and Ravicti™ (glycerol phenylbutyrate) for conditions not outlined in this policy are considered investigational.

Length of Approval

<table>
<thead>
<tr>
<th>Approval</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial authorization</td>
<td>All drugs listed in policy may be approved up to 12 months.</td>
</tr>
<tr>
<td>Re-authorization criteria</td>
<td>Future re-authorization of all drugs listed in policy may be approved up to 3 years as long as the drug-specific coverage criteria are met and chart notes demonstrate that the patient continues to show a positive clinical response to therapy.</td>
</tr>
</tbody>
</table>

Documentation Requirements

The patient’s medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following:

- Office visit notes that contain the diagnosis, relevant history, physical evaluation and medication history

Coding
Related Information

Consideration of Age

The ages stated in this policy for which generic sodium phenylbutyrate, Buphenyl® (sodium phenylbutyrate), Carbaglu® (carglumic acid), and Ravicti™ (glycerol phenylbutyrate) are considered medically necessary are based on the ages approved in the FDA labeling.

Benefit Application

This policy is managed through the Pharmacy benefit.

Evidence Review

Background

Urea Cycle Disorders (UCDs) result from inherited deficiencies of enzymes or transporters including: N-acetylglutamate synthase (NAGS), carbamyl phosphate synthetase (CPS), ornithine transcarbamylase (OTC), argininosuccinate acid synthetase (AS), argininosuccinate acid lyase (ASL), or arginase (ARG). OTC is the most common enzyme deficiency of these disorders. These enzymes are responsible for the synthesis of urea from ammonia (NH3, NH4+). UCDs are rare genetic disorders, and its clinical manifestations are characterized by hyperammonemia and life-threatening hyperammonemic crises. Hyperammonemia-related neurologic injury ranges from lethal cerebral edema to mild cognitive impairment among individuals with milder genetic defects. The goal of management is to control ammonia levels and avoid hyperammonemic crisis. Treatments are directed towards reducing ureagenesis through dietary protein restriction, arginine, or citrilline supplementation, and administration of nitrogen-scavenging drugs.
The deficiency of the enzymes or transporters involved in UCDs varies from patient to patient, and some patients have a total or near total absence of activity of the first four enzymes of the urea cycle (OTC, CPS, AS, and ALS). These deficiencies lead to accumulation of ammonia and other precursor metabolites during the first few days of life. Some patients may have partial absence of the enzymes of the urea cycle, leading to a milder form of the disease. Patients may present with clinical manifestations across the lifespan, including as newborn/infants and in early childhood.

Most patients are diagnosed after presenting symptoms of hyperammonemia. If an elevated blood ammonia level is confirmed, and the results of other routine lab tests are consistent with a UCD diagnosis (normal anion gap, normal blood glucose, absence of liver disease), amino acid levels are tested to establish a specific diagnosis. The laboratory hallmark of a urea cycle disorder (UCD) is an elevated plasma ammonia concentration (>100 to 150 micromol/L).

The initial management of UCDs is to rehydrate and maintain good urine output without overhydrating. The next step is to remove nitrogen (ammonia) from the body using medications and/or hemodialysis. It is important to stop protein intake and minimize catabolism, as well as stimulate anabolism and uptake of nitrogen precursors by muscle. For chronic management of urea cycle disorders, if dietary protein restriction and/or amino acid supplementation cannot manage the disorder alone, then Buphenyl® (sodium phenylbutyrate) is the next option.

**Summary of Evidence**

**Buphenyl® (sodium phenylbutyrate)**

Previously, neonatal-onset disease was almost universally fatal within the first year of life, even when treated with peritoneal dialysis and essential amino acids or their nitrogen-free analogs. However, with hemodialysis, use of alternative waste nitrogen excretion pathways (sodium phenylbutyrate, sodium benzoate, and sodium phenylacetate), dietary protein restriction, and, in some cases, essential amino acid supplementation, the survival rate in newborns diagnosed after birth but within the first month of life is almost 80%. Most deaths have occurred during an episode of acute hyperammonemic encephalopathy.

Patients with neonatal-onset disease have a high incidence of mental retardation. Those who had IQ tests administered had an incidence of mental retardation as follows: ornithine transcarbamylase deficiency, 100% (14/14 patients tested); argininosuccinic acid synthetase deficiency, 88% (15/17 patients tested); and carbamylphosphate synthetase deficiency, 57% (4/7 patients tested). Retardation was severe in the majority of patients. In patients diagnosed during
gestation and treated prior to any episode of hyperammonemic encephalopathy, survival is 100%, but even in these patients, most subsequently demonstrate cognitive impairment or other neurologic deficits. In late-onset deficiency patients, including females heterozygous for ornithine transcarbamylase deficiency, who recover from hyperammonemic encephalopathy and are then treated chronically with sodium phenylbutyrate and dietary protein restriction, the survival rate is 98%. The two deaths in this group of patients occurred during episodes of hyperammonemic encephalopathy. However, compliance with the therapeutic regimen has not been adequately documented to allow evaluation of the potential for sodium phenylbutyrate and dietary protein restriction to prevent mental deterioration and recurrence of hyperammonemic encephalopathy if carefully adhered to. The majority of these patients tested (30/46 or 65%) have IQ’s in the average to low average/borderline mentally retarded range. Reversal of preexisting neurologic impairment is not likely to occur with treatment and neurologic deterioration may continue in some patients. Even on therapy, acute hyperammonemic encephalopathy recurred in the majority of patients for whom the drug is indicated.

Safety

The assessment of clinical adverse events came from 206 patients treated with sodium phenylbutyrate. Adverse events (both clinical and laboratory) were not collected systematically in these patients but were obtained from patient-visit reports by the 65 co-investigators. Causality of adverse effects is sometimes difficult to determine in this patient population because they may result from either the underlying disease, the patient’s restricted diet, intercurrent illness, or sodium phenylbutyrate. Furthermore, the rates may be underestimated because they were reported primarily by parent or guardian and not the patient.

In female patients, the most common clinical adverse event reported was amenorrhea/menstrual dysfunction (irregular menstrual cycles), which occurred in 23% of the menstruating patients. Decreased appetite occurred in 4% of all patients. Body odor (probably caused by the metabolite, phenylacetate) and bad taste or taste aversion were each reported in 3% of patients.

Carbaglu® (carglumic acid)

The efficacy of carglumic acid in the treatment of hyperammonemia due to N-acetylglutamate synthase (NAGS) deficiency was evaluated in a retrospective review of the clinical course of 23 NAGS deficiency patients who received carglumic acid treatment for a median of 7.9 years (range 0.6 to 20.8 years). Treatment with carglumic acid was divided in two regimens. For acute
treatment, patients received a total daily dose of 100 to 250 mg/kg per day primarily administered in 2 to 4 divided doses for the first few days of treatment. For maintenance treatment, the dosage was reduced over time based upon biochemical and clinical responses. The clinical observations in the 23 patient case series were retrospective, unblinded and uncontrolled and preclude any meaningful formal statistical analyses of the data. However, short-term efficacy was evaluated using mean and median change in plasma ammonia levels from baseline to days 1 to 3. Persistence of efficacy was evaluated using long-term mean and median change in plasma ammonia level. Of the 23 NAGS deficiency patients who received treatment with carglumic acid, a subset of 13 patients who had both well documented plasma ammonia levels prior to carglumic acid treatment and after long-term treatment with carglumic acid were selected for analysis.

All 13 patients had abnormal ammonia levels at baseline. The overall mean baseline plasma ammonia level was 271 micromol/L. By day 3, normal plasma ammonia levels were attained in patients for whom data were available. Long-term efficacy was measured using the last reported plasma ammonia level for each of the 13 patients analyzed (median length of treatment was 6 years; range 1 to 16 years). The mean and median ammonia levels were 23 micromol/L and 24 micromol/L, respectively, after a mean treatment duration of 8 years.

**Safety**

Adverse reactions occurring in 2 or more patients treated with carglumic acid in the retrospective case series (≥ 10%) were vomiting (26%), abdominal pain (17%), pyrexia (17%), tonsillitis (17%), anemia (13%), diarrhea (13%), ear infection (13%), infections (13%), nasopharyngitis (13%) and hemoglobin decreased (13%).

**Ravicti™ (glycerol phenylbutyrate)**

Evidence for the efficacy of glycerol phenylbutyrate in treating urea cycle disorder consists of one multicenter, randomized, double-blind, double-dummy, placebo-controlled, cross-over, non-inferiority study. The phase 3 study assessed the non-inferiority of glycerol phenylbutyrate to sodium phenylbutyrate by evaluating blood ammonia levels in adult patients with UCDs from OTC, CPS, and AS who were being treated with sodium phenylbutyrate for control of their UCD. Adult patients ≥18 years of age with diagnoses of UCD were enrolled, an each of the patients had deficiencies including CPS, OTC, or AS, confirmed via enzymatic, biochemical, or genetic testing. They were required to have controlled ammonia levels <100 μmol/L without signs and
symptoms of hyperammonemia. The patients were not allowed to receive drugs known to increase ammonia levels, increase protein catabolism, or significantly affect renal clearance.

The sample size of 46 patients (only 44 patients were used in the analysis portion) were randomized equally to received placebo glycerol phenylbutyrate plus active sodium phenylbutyrate, or placebo sodium phenylbutyrate plus active glycerol phenylbutyrate for 14 days and then crossed over to receive the alternative treatment. The dose of glycerol phenylbutyrate was calculated to deliver the same amount of phenylbutyrate as each patient’s baseline sodium phenylbutyrate dose.

In both randomized groups, the patients received the same amount of phenylbutyrate throughout the study and followed a balanced diet in terms of protein and calorie intake. At the end of each treatment period (2 weeks), patients underwent repeated blood sampling over 24 hours for ammonia plasma and urine levels of metabolites, including phenylbutyrate and phenylacetic acid. The primary efficacy measure was daily ammonia exposure, assessed as 24-hour AUC. Non-inferiority was to be achieved if the upper 95% confidence interval (CI) for the ratio of the least squares means between glycerol phenylbutyrate and sodium phenylbutyrate was less than or equal to 1.25. The non-inferiority margin of 1.25 is consistent with FDA guidance on bioequivalence studies and corresponds to an absolute difference of approximately 9 umol/L for a patient with an ammonia at the upper limit of normal (35 umol/L), a clinically insignificant change.

When administered at the recommended dose levels sodium phenylbutyrate has been shown from clinical experience to be safe and effective in improving long-term survival in patients with UCDs (i.e., reducing the incidence of deaths due to hyperammonemic encephalopathy). However, compliance with sodium phenylbutyrate is difficult due to a high pill burden (up to 40 pills or 40 mL of dissolved powder daily for patients taking 20 g of sodium phenylbutyrate), foul taste, unpleasant odor, and high sodium content (approximately 2,300 mg/day for patients taking 20 g). All of these factors render sodium phenylbutyrate difficult to take, and compliance is suboptimal even for UCD patients with the most severe deficiency states, whose alternative is life-threatening hyperammonemia. Consequently, UCDs remains as a rare, serious and life-threatening condition with a not fully met medical need. Ravicti™ is an alternative therapy to sodium phenylbutyrate in patients with UCDs as it is expected to provide similar nitrogen-scavenging ability while eliminating the current issues of bad taste, odor, sodium content, and pill burden.

Forty patients who completed the short-term adult study and 11 patients who completed the short-term pediatric study enrolled in the long-term protocols; 26 additional, newly-enrolled adult and pediatric patients were also in the long-term protocol for a total of 77 UCD patients (51 adult and 26 pediatric patients ages 6–17, including ARG, ASL, AS, CPS, and OTC subtypes).
Mean ammonia values during long term treatment with glycerol phenylbutyrate were similar to the mean fasting values (time 0 or 24h) observed during the short-term controlled studies and well below the upper limit of normal (35 umol/L) for both pediatric and adult patients at each monthly visit, with monthly means approximately half the upper limit of normal and ranging from 6.3 (Month 9) to 29.6 μmol/L (Month 11).

**Safety**

The most common adverse events were mild gastrointestinal issues. Adverse events were reported by 61% and 51% of patients during glycerol phenylbutyrate and sodium phenylbutyrate treatment, respectively. The gastrointestinal disorders included diarrhea, flatulence, abdominal discomfort, dyspepsia, nausea, and oral discomfort. No clinically significant lab or ECG changes were observed. Headache, somnolence, lightheadedness, and confusion are all possible adverse reactions of glycerol phenylbutyrate. Phenylacetic acid exposure is associated with neurological toxicity at dose-dependent increases manifested by dysgeusia, hypoacusis, disorientation, and impaired memory. One patient experienced a hyperammonemic crisis and one patient withdrew early because of high ammonia and headache; both during sodium phenylbutyrate treatment. One patient had a serious adverse event including gastroenteritis on glycerol phenylbutyrate. There were no deaths during the study.

**References**

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>10/01/19</td>
<td>New policy, approved September 10, 2019. Add to Prescription Drug section. Criteria added for Buphenyl (sodium phenylbutyrate), Carbaglu (carglumic acid), and Ravicti (glycerol phenylbutyrate).</td>
</tr>
<tr>
<td>02/01/20</td>
<td>Interim Review, approved January 9, 2020. Added coverage criteria for generic sodium phenylbutyrate and updated coverage criteria for Buphenyl (sodium phenylbutyrate).</td>
</tr>
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</table>

**Disclaimer:** This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2020 Premera All Rights Reserved.

**Scope:** Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.
Discrimination is Against the Law

Premera Blue Cross complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex. Premera does not exclude people or treat them differently because of race, color, national origin, age, disability or sex.

Premera:
- Provides free aids and services to people with disabilities to communicate effectively with us, such as:
  - Qualified sign language interpreters
  - Written information in other formats (large print, audio, accessible electronic formats, other formats)
- Provides free language services to people whose primary language is not English, such as:
  - Qualified interpreters
  - Information written in other languages

If you believe that Premera has failed to provide these services or discriminate in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance with:

Civil Rights Coordinator - Complaints and Appeals
PO Box 91102, Seattle, WA 98111

You can also file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.


Getting Help in Other Languages

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action before these dates to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost.

Contracts for grievances and the Civil Rights Coordinator are available at


Arabic (العربية):

يحدث هذا الإشعار مستندًا على قمة معلومات حساسة، قد يحتوي على معلومات حساسة تتعلق بجميع طلباتك، أو

Premera Blue Cross. هذه المعلومات مفيدة في تقديم مناسبات للجميع، أو

 поможет في تقديم مناسبات للجميع. هذه المعلومات مفيدة في تقديم مناسبات للجميع، أو

Premera Blue Cross.

Italiano (Italian):


中文 (Chinese):

本通知有重要的訊息。本通知可能有關於您透過 Premera Blue Cross 提交的申請或保險的重要訊息。本通知可能有重要日期。您可能需要在截止日期之前採取行動。以保留您的健康保險或者費用補貼。您有權利免費以您的母語得到本訊息和幫助。請撥電話 800-722-1471 (TTY: 800-842-5357)。

Oromo (Cushite):

Talvez seja necessário que você tome providências dentro de
do Premera Blue Cross. Poderão existir datas importantes neste aviso.
informações importantes a respeito de sua aplicação ou cobertura por meio

rho (Lao):

Laotian (Lao):

Premera Blue Cross ທ່ານເຫຼືອງຈາກພະລັງສາຍຊົນເລ້ນ ສູ່ພະຫີນພະພາບຂອງທ່ານໄດ້ຖືກຕ້ອງການ ັິ່ງໝອກພະບາຍນາມຂອງທ່ານໄດ້ຖືກຕ້ອງການ ທີ່ເອງຈາກພະລັງສາຍຊົນເລ້ນ ສູ່ພະຫີນພະພາບຂອງທ່ານໄດ້ຖືກຕ້ອງການ ັິ່ງໝອກພະບາຍນາມຂອງທ່ານໄດ້ຖືກຕ້ອງການ ັິ່ງໝອກພະບາຍນາມຂອງທ່ານໄດ້ຖືກຕ້ອງການ ັິ່ງໝອກພະບາຍນາມຂອງທ່ານໄດ້ຖືກຕ້ອງການ ັິ່ງໝອກພະບາຍນາມຂອງທ່ານໄດ້ຖືກຕ້ອງການ ແຈ້ງການນ້ີ ນສໍ

Tagalog (Tagalog):


&lt;span&gt;&lt;/span&gt;

Thai (Thai):

ไทยที่ใช้ภาษาต่างๆ ประกาศนี้มีข้อมูลสำคัญเกี่ยวกับการขอรับการคุ้มภัยต่างๆ ของสุขภาพของคุณ Premera Blue Cross และคุณอาจต้องทราบข้อมูลเกี่ยวกับการคุ้มภัยต่างๆ ของสุขภาพของคุณ Premera Blue Cross ที่ใช้ภาษาต่างๆ ประกาศนี้มีข้อมูลสำคัญเกี่ยวกับการขอรับการคุ้มภัยต่างๆ ของสุขภาพของคุณ Premera Blue Cross และคุณอาจต้องทราบข้อมูลเกี่ยวกับการคุ้มภัยต่างๆ ของสุขภาพของคุณ Premera Blue Cross ที่ใช้ภาษาต่างๆ ประกาศนี้มีข้อมูลสำคัญเกี่ยวกับการข้อมูลเกี่ยวกับการคุ้มภัยต่างๆ ของสุขภาพของคุณ Premera Blue Cross และคุณอาจต้องทราบข้อมูลเกี่ยวกับการคุ้มภัยต่างๆ ของสุขภาพของคุณ Premera Blue Cross ที่ใช้ภาษาต่างๆ ประกาศนี้มีข้อมูลสำคัญเกี่ยวกับการขอรับการคุ้มภัยต่างๆ ของสุขภาพของคุณ Premera Blue Cross และคุณอาจต้องทราบข้อมูลเกี่ยวกับการคุ้มภัยต่างๆ ของสุขภาพของคุณ Premera Blue Cross ที่ใช้ภาษาต่างๆ ประกาศนี้มีข้อมูลสำคัญเกี่ยวกับการขอรับการคุ้มภัยต่างๆ ของสุขภาพของคุณ Premera Blue Cross และคุณอาจต้องทราบข้อมูลเกี่ยวกับการคุ้มภัยต่างๆ ของสุขภาพของคุณ Premera Blue Cross ที่ใช้ภาษาต่างๆ ประกาศนี้มีข้อมูลสำคัญเกี่ยวกับการขอรับการคุ้มภัยต่างๆ ของสุขภาพของคุณ Premera Blue Cross และคุณอาจต้องทราบข้อมูลเกี่ยวกับการคุ้มภัยต่างๆ ของสุขภาพของคุณ Premera Blue Cross ที่ใช้ภาษาต่างๆ ประกาศนี้มีข้อมูลสำคัญเกี่ยวกับการขอรับการคุ้มภัยต่างๆ ของสุขภาพของคุณ Premera Blue Cross และคุณอาจต้องทราบข้อมูลเกี่ยวกับการคุ้มภัยต่างๆ ของสุขภาพของคุณ Premera Blue Cross ที่ใช้ภาษาต่างๆ ประกาศนี้มีข้อมูลสำคัญเกี่ยวกับการขอรับการคุ้มภัยต่างๆ ของสุขภาพของคุณ Premera Blue Cross และคุณอาจต้องทราบข้อมูลเกี่�

Korean (Korean):

Japanese (Japanese):

Premera Blue Cross'の申請または補償範囲に関する重要な情報が含まれています。この通知には記載されている情報が重要な日を確認してください。健康保険や資料サポートを維持するには、特定の日本語で動作を

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Turkish (Vietnamese):