

# Clinical Policy: Hyperemesis Gravidarum Treatment

Reference Number: CP.MP.34

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See [Important Reminder](#) at the end of this policy for important regulatory and legal information.

## Description

Hyperemesis gravidarum is a term reserved to describe the most severe cases of nausea and vomiting in pregnancy (NVP). It results from severe nausea and vomiting, and the resultant inability to rehydrate and replenish nutritional reserves. A diagnosis of hyperemesis gravidarum is best made when it is based on objective findings such as moderate to large ketonuria and weight loss. Weight loss of 5% or greater is often described as diagnostic of hyperemesis gravidarum but this is not to suggest that measures to improve nausea and vomiting should not be undertaken prior to this. Hyperemesis gravidarum tends to begin earlier in pregnancy and last longer than those patients with less severe NVP.

When the step-approach algorithm does not allow for continued adequate hydration of the patient, intravenous (IV) infusion or subcutaneous (SQ) micropump infusion of ondansetron can allow for treatment until the patient can reliably take oral medications. The ability to perform activities of daily living, tolerate most food intake, and take oral medications are measures that objectively and subjectively instruct the practitioner as to the value of these therapies. When these therapies have allowed the patient to return to the above states of function, they can be discontinued. Oral therapies can be used in conjunction with IV and SQ infusion if tolerated. There is not a place for continuous, long-term IV or SQ infusion of medications to manage hyperemesis if the patient is functioning as described above.

## Policy/Criteria

- I. It is the policy of health plans affiliated with Centene Corporation<sup>®</sup> that hyperemesis gravidarum treatment is **medically necessary** when meeting the following criteria:
  - A. *IV infusion of metoclopramide or ondansetron, or SQ micropump infusion of ondansetron* for the treatment of intractable hyperemesis gravidarum (must meet all):
    1. Failed at least one drug in each step of the step therapy approach in Table 1 below;
    2. Other potential causes of nausea and vomiting have been ruled out;
    3. Clinical signs of hyperemesis gravidarum, including nausea and vomiting, have been persistent for  $\geq 3$  weeks;
    4. Within this time there has been documented weight loss and dehydration or electrolyte abnormalities.

Infusion may be approved at 2-week intervals based on the patient's response to therapy.

1. Non-responder - If no improvement with injectable/IV antiemetics, they should be discontinued.
2. Responder - When the patient has minimal vomiting and nausea and no dehydration for five days, therapy can be discontinued.
3. Partial responder - If the patient does not meet non-responder or responder criteria, the therapy should continue. An additional 10-14 days are recommended before further reauthorization is required.

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- B. Home enteral therapy** for maternal weight loss secondary to hyperemesis (must meet all):
1. Attempted and failed the step therapy approach listed in Table 1 below;
  2. Other potential causes of nausea and vomiting have been ruled out;
  3. Clinical signs of hyperemesis gravidarum, including nausea and vomiting, have been persistent for  $\geq 3$  weeks;
  4. Within this time, there has been documented weight loss and dehydration or electrolyte abnormalities;
  5. Enteral therapy is started in the hospital.

Therapy may be approved at intervals of 5 to 21 days, based on the individual member's needs.

- C. Parenteral therapy with home total parenteral nutrition (TPN)** for the management of intractable hyperemesis gravidarum (must meet all):
1. Other potential causes of nausea and vomiting have been ruled out;
  2. Clinical signs of hyperemesis gravidarum, including nausea and vomiting, have been persistent for  $\geq 3$  weeks;
  3. Within this time, there has been documented weight loss and dehydration or electrolyte abnormalities;
  4. There has been  $> 5\%$  weight loss since the beginning of pregnancy and the member is over 14 weeks pregnant;
  5. The patient has failed IV or SQ Zofran or IV Reglan therapy;
  6. The patient has failed, or is not a candidate for, enteral therapy (nausea is unrelated to olfactory or gustatory cues);
  7. The member has been informed of and fully consented to the risks of line infection, bacteremia, sepsis, thrombosis, and fetal loss;
  8. A peripherally inserted central catheter (PICC) line is started in the hospital.

Therapy may be approved at intervals of 5 to 14 days based on the individual member's needs.

### Background

Hyperemesis gravidarum and NVP are self-limiting problems given appropriate time, dietary adjustments, intensive support, and counseling. The presentation is often a symptomatic issue and not an issue of dehydration. Intense nausea with small amounts of emesis needs to be differentiated from true hyperemesis and associated dehydration. Therapeutic decisions should be based on the clinical presentation and objective findings.

Step-therapy approaches that begin with monotherapy and add medicines with different mechanisms of anti-emetic action are the most effective treatment regimes. A step-therapy algorithm should result in satisfactory treatment for the majority of patients with "hypernausea" or hyperemesis gravidarum. Time, oral intake, psychotherapy, education, and intensive support should allow for the patient to eventually return to a state where she can again function and eat properly.

*Table 1: Nausea and vomiting in pregnancy step-therapy*

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If there is not improvement after the first step, proceed to the next. Dosages and frequency may be adjusted based on tolerability and improvement in symptoms.

- Initial therapy, one of the following:
  - Pyridoxine (vitamin B<sub>6</sub>) 10-25 mg by mouth (PO) every 6-8 hours;
  - Ginger 250 mg capsules four times daily;
  - Pyridoxine (vitamin B<sub>6</sub>) 10-25 mg and doxylamine (Unisom) (**Note:** an extended-release combination product is preferred)
    - Pyridoxine 10-25 mg and doxylamine 12.5 mg PO every 6-8 hours (equivalent to Diclegis);
    - Pyridoxine 10mg and doxylamine 10mg combination product, 2 tablets at bedtime, up to 4 daily
    - Pyridoxine 20mg and doxylamine 20mg combination product, 1 tablet at bedtime, up to 2 daily
  - Dimenhydrinate (Dramamine) 25-50 mg PO every 4-6 hours;
  - Promethazine 12.5 – 25 mg PO, rectal suppository or IM every 4-6 hours;
  - Prochlorperazine 5 to 10 mg PO, IM or IV every 6 -8 hours, or 25 mg rectally twice daily;
  - Diphenhydramine 25 to 50 mg PO or 10 to 50 mg IV every 4 to 6 hours as needed;
  - Meclizine 25 mg PO every 4 to 6 hours as needed.
  - Trimethobenzamide 200 mg every 6-8 hours, IM
- Step 2, one of the following:
  - Metoclopramide (Reglan) 5 - 10 mg PO, intramuscularly, or IV, three times daily or four times daily;
  - Ondansetron (Zofran) 4 or 8 mg PO twice daily or three times daily. Zofran oral disintegrating tablets may be more useful.
  - Dimenhydrinate 50 mg IV (in 50 ml saline, over 20 minutes), every 4-6 hours
  - Promethazine, 12.5-25 mg IV every 4-6 hours

Failed outpatient management, multiple hospitalizations, electrolyte disturbances, and/or persistent weight loss might necessitate long term venous access for fluid and electrolyte replacement and possible supplemental nutrition. The overall percentage of patients with nausea and vomiting in pregnancy requiring parenteral nutrition or IV anti-emetic therapy is very small.

#### *Complications*

Hyperemesis gravidarum and its effects are rarely the cause of fetal morbidity or mortality or of maternal mortality. It is the most common cause of hospitalization in the first half of the pregnancy.

Other reported maternal complications of hyperemesis gravidarum are:

- Wernicke's encephalopathy
- Beriberi
- Central pontine myelinolysis
- Hepatic insufficiency
- Acute tubular necrosis
- Peripheral neuropathy
- Traumatic damage to the esophagus, retina, or spleen secondary to vomiting

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#### *Management*

There is no single accepted method of management of NVP and hyperemesis gravidarum. Commonalities are the treatment of the nausea itself, hydration, and alteration in diet. Frequent, small meals, higher protein, lower carbohydrate meals, and meals that are higher in liquid content all have some scientific validity as a means to lessen the problem.

Fear of medication is one of the most common reasons for under-treatment of NVP. This may come from the patient, her family, or the medical office. The common oral therapies have been shown to be safe. There is more potential for harm when there is untreated hyperemesis gravidarum that leads to hospitalization and risk for iatrogenic problems such as IV site infection, versus treatments for hyperemesis gravidarum. Untreated hyperemesis gravidarum also increases the chance that an underlying undiagnosed problem other than NVP could worsen.

There is one FDA-approved prescription drug for the treatment of NVP, Diclegis, which was approved on April 9, 2013. Diclegis is a combination of doxylamine succinate 10mg and pyridoxine hydrochloride (Vit B6) 10mg. Doxylamine and pyridoxine are both available in over-the-counter formulations. Off-label uses of many other drugs have been supported by the literature and ACOG in regards to safety.

The safety of ondansetron for NVP has been questioned, and was most recently evaluated in a retrospective review of 1.8 million women enrolled in Medicaid from three months before to one month after delivery. After accounting for confounders, the risk of cardiac or congenital malformations overall was not increased with first-trimester exposure to ondansetron. However, there was a small increase (2.7 in 10,000 births) in the incidence of oral cleft. Given the small increased risk, and the apparent efficacy for treating NVP, ondansetron may be classified as an appropriate treatment option after other options have failed.

Gastroesophageal reflux can affect up to 50% of pregnancies. Associated symptoms are heartburn, belching, nausea, and early satiety. A therapeutic trial of ranitidine is safe and often effective. There is the possibility of mild underlying chronic gastric problems such as gastritis. These would be undetected and the patient would not be a candidate for endoscopy.

Step-therapy approaches that add medicines with different mechanisms of anti-emetic action are the most effective treatment regimes. Decisions as to the need for home IV hydration should be made alongside decisions for treatment of nausea and vomiting. IV hydration alone, with SQ/IV medication, or following SQ/IV medication regimes often play a necessary role. Clinicians should include measures of hydration (specific gravity, rapid weight loss, ketonuria) in their assessment of the patient's status and not rely only on the verbal reports of nausea and vomiting when considering ongoing care. When considering long term IV or SQ access for severe hyperemesis treatment, the risks must be weighed against the benefits carefully. Risks of PICC line complications in the gravid patient have been documented.

A 2007 study<sup>4</sup> looked at three treatment methods for ninety-four patients that were stratified into: 1) management with intravenous medication alone, 2) management with nasogastric or nasoduodenal tube, and 3) management with placement of a PICC line. The enteral and parenteral nutrition patients also had medical therapy. All of the patients in the IV therapy arm

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had at least two medications. Five of the thirty-three patients with a PICC line also had TPN. Each patient was admitted for the treatment of nausea and vomiting, ketonuria, and electrolyte disturbances. The authors described the differences as “striking.” The study showed that serious complications, i.e., bacteremia, sepsis, and thrombosis, were observed in the *majority* of the PICC line group. There were three fetal losses in the PICC line group, including an intrauterine demise at 20 weeks that resulted from infection of a PICC line placed at 12 weeks. There were no significant differences in neonatal outcomes in regards to fetal weight at delivery, gestational age at delivery, and Apgar scores. There were more admissions to the NICU in the PICC line group. The authors concluded that due to severe, life-threatening complications, the use of “PICC lines for the management of hyperemesis is rarely indicated and, except in specific circumstances, should be avoided.”

A nutritional strategy that is often underutilized is enteral feeding using pediatric nasogastric tubes. This has been used with success in patients with intractable nausea, vomiting, weight loss, and hospitalization. One study<sup>5</sup> looked at seven patients who had strong gustatory and olfactory cues who used enteral feedings. In each case there was improvement within 24 hours. Six patients were discharged with continued out-patient enteral feeds. Oral liquids were tolerated by all patients within 2-5 days.

In an updated practice bulletin, ACOG reports, “There is limited evidence regarding the clinical efficacy of the use of continuous subcutaneous microinfusion pumps to administer metoclopramide or ondansetron for the treatment of nausea and vomiting of pregnancy. Moreover, adverse effects with the use of continuous subcutaneous pumps were seen in 11–31% of selected patients.”<sup>12</sup> In addition, UpToDate does not recommend the use of a SQ pump for delivery of metoclopramide, however, Zofran via a microinfusion pump appears to be a reasonable alternative route for treating severe nausea and vomiting of pregnancy, although adverse side effects are common.<sup>10</sup> Both conclude that SQ microinfusion pumps of these antiemetic therapies do not appear to be cost effective when compared with conventional treatment alternatives, including periodic hospitalization. Ondansetron and metoclopramide IV are both included in the treatment algorithm for persistent symptoms.

**Coding Implications**

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CPT® Codes	Description
96360	Intravenous infusion, hydration; initial, 31 minutes to 1 hour
96361	Intravenous infusion, hydration; each additional hour (List separately in addition to code for primary procedure)

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<b>HCPCS Codes</b>	<b>Description</b>
J1240	Injection, dimenhydrinate, up to 50 mg
J2405	Injection, ondansetron HCl, per 1 mg
J2765	Injection, metoclopramide HCl, up to 10 mg
S9351	Home infusion therapy, continuous or intermittent antiemetic infusion therapy; administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and visits coded separately), per diem
S9364	Home infusion therapy, total parenteral nutrition (TPN); administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment including standard TPN formula (lipids, specialty amino acid formulas, drugs other than in standard formula and nursing visits coded separately), per diem (do not use with home infusion codes S9365-S9368 using daily volume scales)
S9365	Home infusion therapy, total parenteral nutrition (TPN); 1 liter per day, administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment including standard TPN formula (lipids, specialty amino acid formulas, drugs other than in standard formula and nursing visits coded separately), per diem
S9366	Home infusion therapy, total parenteral nutrition (TPN); more than 1 liter but no more than 2 liters per day, administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment including standard TPN formula (lipids, specialty amino acid formulas, drugs other than in standard formula and nursing visits coded separately), per diem
S9367	Home infusion therapy, total parenteral nutrition (TPN); more than 2 liters but no more than 3 liters per day, administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment including standard TPN formula (lipids, specialty amino acid formulas, drugs other than in standard formula and nursing visits coded separately), per diem
S9368	Home infusion therapy, total parenteral nutrition (TPN); more than 3 liters per day, administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment including standard TPN formula (lipids, specialty amino acid formulas, drugs other than in standard formula and nursing visits coded separately), per diem

**ICD-10-CM Diagnosis Codes that Support Coverage Criteria**

<b>ICD 10 CM Code</b>	<b>Description</b>
E51.11-E51.12	Beriberi (Dry and/or wet)
E51.2	Wernicke's encephalopathy
E86.0	Dehydration
E87.8	Other disorders of electrolyte and fluid balance, not elsewhere classified
G37.2	Central pontine myelinolysis
K72.00	Acute and subacute hepatic failure without coma

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ICD 10 CM Code	Description
N17.0	Acute kidney failure with tubular necrosis
O21.0	Mild hyperemesis gravidarum
O21.1	Hyperemesis gravidarum with metabolic disturbance
O21.2	Late vomiting of pregnancy
O26.821-O26.823	Pregnancy related peripheral neuritis (1 <sup>st</sup> , 2 <sup>nd</sup> &/or 3 <sup>rd</sup> trimester)
R63.4	Abnormal weight loss
R82.4	Acetonuria (Ketonuria)

Reviews, Revisions, and Approvals	Date	Approval Date
Policy developed		03/09
Added Diclegis as new FDA approved drug for hyperemesis and clarified that Doxylamine and pyridoxine are both available as OTC meds	5/13	6/13
References reviewed and updated	6/14	6/14
Moved majority of description information to background section Converted Algorithm for treatment into Table 1 Reorganized policy/criteria section into appropriate numbering bullets and reworded section. Clarified approval intervals language. Removed prognosis and differential diagnosis sections. Clarified step therapy requirements into 2 steps	6/15	6/15
Converted to new template Added promethazine, prochlorperazine, diphenhydramine and meclizine to initial step therapy per UpToDate treatment algorithm. Reviewed by specialist.	5/16	06/16
Minor wording changes to background for clarity. References reviewed and updated.	06/17	06/17
Removed SQ micropump infusion of metoclopramide from section: Description, 1.A and C.7. Revised dosage of Dimenhydrinate in table 1, initial therapy as per ACOG/UTD. Added Trimethobenzamide IM to initial therapy table 1 per ACOG. Added Dimenhydrinate IV to Step 2 in Table 1 per ACOG. Background updated with language from ACOG Practice Bulletin #189. HCPCS codes updated.	02/18	02/18
Removed step therapy approach in I.C because it is redundant. Removed: Information about symptoms, food intake, urinary ketones, urine specific gravity, and daily weights is supplied from A, B, & C as this is not specific criteria rather just medical records.	03/18	
Added pyridoxine and doxylamine dosing options for 10/10 mg tabs 2-4 times daily, and 20/20mg tabs 1-2 times daily, per ACOG. Updated background regarding ondansetron use.	01/19	02/19
Background: Under step therapy Step 1 section on pyridoxine/doxylamine, noted that an extended release pyridoxine/doxylamine combination product is preferred. Other minor revisions to the background with no impact on criteria. References reviewed and updated. Specialist review.	12/19	2/20

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**Important Reminder**

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or



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