INSTRUCTIONS FOR USE

This protocol provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the enrollee specific document must be referenced. The terms of an enrollee’s document (e.g., Certificate of Coverage (COC) or Evidence of Coverage (EOC)) may differ greatly. In the event of a conflict, the enrollee's specific benefit document supersedes this protocol. All reviewers must first identify enrollee eligibility, any federal or state regulatory requirements and the plan benefit coverage prior to use of this Protocol. Other Protocols, Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its’ Protocols, Policies and Guidelines as necessary. This protocol is provided for informational purposes. It does not constitute medical advice. This policy does not govern Medicare Group Retiree members.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

COMMERCIAL and MEDICARE COVERAGE RATIONALE

Tocolytic Therapy
The use of tocolytic therapy beyond 48 hours is not medically necessary for preventing spontaneous preterm birth by prolonging pregnancy. Available studies fail to demonstrate any benefit of maintenance tocolysis in terms of gestational age at birth, pregnancy prolongation or birth weight.

Subcutaneous terbutaline pump maintenance therapy is not medically necessary for delaying or preventing spontaneous preterm birth by prolonging pregnancy. Terbutaline pump maintenance therapy has not been shown to decrease the risk of preterm birth by prolonging pregnancy.

Magnesium sulphate is medically necessary for treating preterm labor short-term when the following criteria are met:
• Short-term prolongation of pregnancy (up to 48 hours) to allow for the administration of antenatal corticosteroids in pregnant women who are at risk of preterm delivery within 7 days OR

• Fetal neuroprotection before anticipated early preterm (less than 32 weeks of gestation) delivery.

**Home Uterine Activity Monitoring**
Home uterine activity monitoring (HUAM) is not medically necessary for preventing spontaneous preterm birth. There is insufficient clinical evidence that home uterine activity monitoring, as an independent variable, reduces the frequency of preterm births. Available studies fail to demonstrate that the use of HUAM reduces the rate of preterm delivery and neonatal complications or improves pregnancy outcomes.

Medicare does not have a National Coverage Determination (NCD) for Preterm Labor Management. Local Coverage Determinations (LCDs) do not exist at this time. Accessed August 2016.

**For Medicare and Medicaid Determinations Related to States Outside of Nevada:**
Please review Local Coverage Determinations that apply to other states outside of Nevada.
http://www.cms.hhs.gov/mcd/search

**Important Note:** Please also review local carrier Web sites in addition to the Medicare Coverage database on the Centers for Medicare and Medicaid Services’ Website.

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**MEDICAID COVERAGE RATIONALE**

**Home-Based (outpatient) Terbutaline Infusion Pump Therapy**
Terbutaline infusion pump therapy is a covered benefit when the following conditions are met:
1. The recipient is at high risk for preterm labor and delivery based on one or a combination of factors:
   a. Current diagnosis of preterm labor with uterine contractions of four or more per hour and progressive cervical change;
   b. Cervical dilatation is less than four centimeters;
   c. History of preterm labor/delivery with previous pregnancies.
2. The recipient is currently or has recently been under treatment to prevent preterm labor with a combination of the following methods:
   a. Bed rest or restricted activity;
   b. Oral tocolytic therapy (document ineffectiveness);
   c. Increased office visits or phone contact for counseling;
   d. Hospitalization.
3. Appropriate alternative treatment has been tried and was not successful or was contraindicated.
4. Physician states recipient is capable of complying with home Terbutaline infusion pump therapy.
5. Recipient is not less than 20 weeks gestation or more than 37 weeks gestation.
6. Fetus is alive and well with an estimated weight of less than 2,500 grams.
7. Costs associated with Terbutaline infusion pump therapy do not exceed $240/day.

**Home Uterine Activity Monitor (HUAM)**
1. Recipient has a current diagnosis of pre-term labor and a history of previous pre-term labor/delivery with pregnancies.
2. Records from physician showing pre-term labor with uterine contractions of four or more per hour and progressive cervical changes.
3. Cervical dilation is less than four centimeters.
4. Recipient is ordered on bedrest or restricted activities.
5. Tocolytic therapy initiated (oral, subcutaneous, or intravenous route).
6. Documentation will show there is an increase in physician/patient contact due to pre-term labor symptoms.
7. The recipient is, in the opinion of the physician, capable of complying with the home monitoring program.
8. Recipient is not less than 24 weeks gestation or more than 37 weeks gestation.

**DESCRIPTION OF SERVICES**

Preterm labor is defined as regular uterine contractions, associated with cervical change, before 37 weeks of gestation. Deliveries that are early by five weeks or more are the leading cause of infant morbidity and mortality in the United States. Preterm labor risk factors include, but are not limited to previous premature birth, current multiple gestations, smoking, previous confirmed preterm labor during current pregnancy and/or shortened cervix.

Despite the introduction of new diagnostic and therapeutic technologies, there has been little reduction in the incidence of preterm birth over the past 30 years. While no treatment has proven highly effective in preventing preterm delivery in women who experience preterm labor, diagnosis at an early stage allows the use of interventions that may delay delivery for 48 hours or more.

Tocolytics are drugs given to inhibit uterine contractions. Acute tocolysis is used to decrease or stop uterine contractions and slow or halt cervical change in women during preterm labor. Maintenance tocolysis refers to medication administered after acute tocolysis, in women with arrested preterm labor, to prevent a recurrence of preterm labor.

The therapeutic agents currently thought to be clearly associated with improved neonatal outcomes include antenatal corticosteroids, for maturation of fetal lungs and other developing organ systems, and the targeted use of magnesium sulfate for fetal neuroprotection.

**CLINICAL EVIDENCE**

**Tocolytic Therapy**

A meta-analysis by Han et al. (2010) did not show any differences between magnesium sulfate maintenance therapy and either placebo or beta-adrenergic receptor agonists in preventing preterm birth after an initial treated episode of threatened preterm labor.

In a Cochrane systematic review, Chawanpaiboon et al. (2014) evaluated the effectiveness of terbutaline pump maintenance therapy after threatened preterm labor in reducing adverse neonatal outcomes. This report replaces an earlier Cochrane review by Nanda et al. (2002). Four randomized controlled trials (n=234) comparing terbutaline pump therapy with alternative therapy, placebo or no therapy after arrest of threatened preterm labor were included in the review. The authors found no strong evidence that terbutaline maintenance therapy offered any advantages over saline placebo or
oral terbutaline maintenance therapy in reducing adverse neonatal outcomes by prolonging pregnancy among women with arrested preterm labor.

In a Cochrane systematic review, Dodd et al. (2012) assessed the effects of oral betamimetic maintenance therapy after threatened preterm labor for preventing preterm birth. The selection criteria were randomized controlled trials comparing oral betamimetic with alternative tocolytic therapy, placebo or no therapy for maintenance following treatment of threatened preterm labor. Thirteen randomized controlled trials (RCTs) were included. The authors concluded that the available evidence does not support the use of oral betamimetics for maintenance therapy after threatened preterm labor.

Padovani et al. (2015) compared the impact of terbutaline versus nifedipine on inhibition of uterine contractions, preterm birth, neonatal sepsis, intracranial hemorrhage or necrotizing enterocolitis, death or admission to a neonatal intensive care unit and maternal adverse reactions. The randomized trial (n=66) was performed in three centers in Brazil between August 2010 and March 2012. Thirty two obstetrical patients received nifedipine 20mg orally and after 30 minutes a second dose was given if contractions did not stop. Once tocolysis was achieved, nifedipine 20 mg orally was administered every 8 hours for a period of 48 hours. Thirty four patients received terbutaline (ampoule 0.5 mg/mL): intravenous infusion of 2.5 lg/min. followed by an increase of 2.5 lg/min. every 15 minutes to a maximum of 20 lg/min. When the minimum dose that stopped contractions was established, the infusion was maintained for 24 hours. After 24 hours of drug administration, the dose was decreased by 2.5 lg/min. every 15 minutes and discontinued. They found no difference between groups in tocolysis or preterm birth. Less serious maternal adverse effects less common with terbutaline included flushing (2.94% versus 43.7%) and headache (5.9% versus 31.2%). The administration of terbutaline increased tremor (76.4% versus 0%), nausea (58.8% versus 9.4%) and dizziness (29.4% versus 6.25%). Each drug has specific side effects, although overall, nifedipine was associated with fewer adverse effects. The authors concluded that the results of this study support previous evidence suggesting that nifedipine is as effective as terbutaline in its impact on tocolysis and neonatal outcome with fewer maternal and fetal adverse effects. The significance of this study is limited by its small sample size.

Theplib and Phupong (2016) conducted a retrospective study (n=385) to determine terbutaline success rate in postponing preterm labor for 48 hours and to identify factors associated with its efficacy, side effects, maternal and neonatal outcomes. They analyzed data from pregnant women suffering from preterm labor who had received terbutaline for inhibition of labor from January 2007 to December 2013. Of the 385 cases, 83.4% delivered ≥48 hours and 16.6% delivered before 48 hours. The factors that affect the success rate of terbutaline administration in singleton pregnancy were cervical dilatation and cervical effacement. The most common side effect of terbutaline was tachycardia (95.1%), and there were no serious cardiovascular events or maternal death. Mean neonatal birth weight was 5 pounds. Neonatal complications included respiratory distress syndrome 16.2%, intraventricular hemorrhage 1.4%, necrotizing enterocolitis 0.7%, sepsis 5.3%, and neonatal death 0.9%. The authors concluded that the success rate of terbutaline in treatment of preterm labor was high, side effects were tolerable and terbutaline can be used safely for short-term treatment of preterm labor.

Klauser et al. (2016) conducted a single center, randomized trial with 92 patients in preterm labor with advanced cervical dilation (4-6cm) to compare the efficacy of tocolytic treatment with indomethacin, magnesium sulfate and nifedipine for acute tocolysis. Secondary analysis of women with advanced cervical dilation (cervix 4-6cm) at 24-32 weeks' gestation who received intravenous magnesium
sulfate, oral nifedipine or indomethacin suppositories comprised this study population. The patients were randomized to one tocolytic type. Days gained in utero (11.7) and percent remaining undelivered at 48h (60.8%), 72h (53.1%) and >7 days (38.3%) were similar regardless of tocolytic utilized. The gestational age at delivery (30.7±3.2) was similar between groups and neonatal statistics were not different. The authors concluded that all three tocolytics offered significant days gained in utero after therapy and a high percentage remaining undelivered after 48 or 72h and after 7 days.

Home Uterine Activity Monitoring (HUAM)

Home uterine activity monitoring (HUAM) uses a device to measure uterine activity away from the clinic or hospital. It is used to detect early-stage uterine contractions suggestive of preterm labor.

According to a multicenter study by the National Institute of Child Health and Human Development (NICHD), portable monitors that detect contractions of the uterus do not appear to be useful for identifying women likely to have a preterm delivery. "Although they are widely prescribed for women at risk of giving birth prematurely, the monitors are not useful for predicting or preventing preterm birth" (Iams et al., 2002).

In a Cochrane systematic review, Urquhart et al. (2012) evaluated whether home uterine activity monitoring is effective in improving outcomes for women and their infants considered to be at high risk of preterm birth. Fifteen randomized control trials (n=6008) were included in the review. The authors found that home uterine monitoring may result in fewer admissions to a neonatal intensive care unit but more unscheduled antenatal visits and tocolytic treatment. The report concluded that home uterine activity monitoring had no impact on maternal and perinatal outcomes such as perinatal mortality or incidence of preterm birth. Updated 2015 with no change to conclusions.

Reichmann (2009) systematically reviewed 3 Level I randomized, controlled trials; 1 level II matched cohort trial; and 5 level III case series evaluating home uterine activity monitoring in multiple gestations and found that contractions in multiple gestations are not predictive of preterm birth. In an earlier review, the same author analyzed published clinical trials examining HUAM for the management of current preterm labor. He concluded that HUAM has no clinical value, has virtually no scientific support and constitutes a gross deviation from evidence-based medicine (Reichmann).

Neuroprotective Effects of Magnesium Sulfate

Doyle et al. (2009) systematically reviewed rates of neurologic outcomes reported in childhood for preterm fetus exposed to antenatal magnesium sulfate. Five eligible randomized controlled trials (RCTs) with 6,145 fetuses were identified; in four studies (4,446 fetuses) the primary intent was neuroprotection of the fetus. Antenatal magnesium sulfate therapy given to women at risk of preterm birth substantially reduced the risk of cerebral palsy in their children. Moreover, there was a significant reduction in the rate of substantial gross motor dysfunction. No statistically significant effect of antenatal magnesium sulfate therapy was detected on pediatric mortality, or on other neurologic impairments or disabilities in the first few years of life. There were no significant effects of antenatal magnesium sulfate on combined rates of mortality with neurologic outcomes, except in the studies where the primary intent was neuroprotection, where there was a reduction in death or cerebral palsy. Two subsequent meta-analyses of similar design confirmed these results (Conde-Agudelo and Romero, 2009; Costantine and Weiner, 2009).
In a multicenter, placebo-controlled, double-blind trial, Rouse et al. (2008) randomly assigned 2241 women at imminent risk for delivery between 24 and 31 weeks of gestation to receive intravenous magnesium sulfate or matching placebo. The primary outcome was a total of stillbirth or infant death by 1 year or moderate or severe cerebral palsy at or beyond 2 years. Fetal exposure to magnesium sulfate before anticipated early preterm delivery did not reduce the combined risk of moderate or severe cerebral palsy or death, although the rate of cerebral palsy was reduced among survivors.

Marret et al. (2007) evaluated whether magnesium sulphate (MgSO₄) given to women at risk of very-preterm birth would be neuroprotective in preterm newborns and would prevent neonatal mortality and severe white matter injury (WMI). 564 gravid women (688 infants) with fetuses of gestational age < 33 weeks whose birth was planned or expected within 24 hours were randomly assigned to receive a single infusion of MgSO₄ or a placebo. The primary outcome was infant death or severe WMI. The investigators found no significant differences in total infant death or severe WMI or both between the two treatment groups and acknowledged that more research is needed to assess the protective effect of MgSO₄ alone or in combination with other neuroprotective molecules.

Crowther et al. (2003) reported the results of a multicenter randomized controlled study evaluating the effectiveness of magnesium sulfate given for neuroprotection to women at risk of preterm birth. A total of 1062 women (1255 infants) with fetuses younger than 30 weeks’ gestation for which birth was planned or expected within 24 hours were enrolled. Women were randomly assigned to receive an infusion of magnesium sulfate or a placebo for 20 minutes followed by a maintenance infusion for up to 24 hours. Primary outcomes included infant death or cerebral palsy or both at a corrected age of 2 years. No significant reductions in the occurrences of infant death or cerebral palsy or both were seen with the magnesium sulfate treatment. In a secondary analysis, the researchers demonstrated significantly less frequent substantial gross motor dysfunction (inability to walk without assistance) or death or both in the infants exposed to magnesium sulfate. Magnesium sulfate given to women immediately before very preterm birth may improve important pediatric outcomes. No serious harmful effects were seen.

Professional Societies

American College of Obstetricians and Gynecologists (ACOG)

A practice bulletin on the management of preterm labor makes the following recommendations based on good and consistent scientific evidence (ACOG 2016a):

- No evidence exists to support the use of home uterine activity monitoring to prevent preterm delivery in women with contractions but no cervical change.
- Accumulated available evidence suggests that magnesium sulfate reduces the severity and risk of cerebral palsy in surviving infants if administered when birth is anticipated before 32 weeks of gestation.
- Evidence supports the use of first-line tocolytic treatment for short-term prolongation of pregnancy (up to 48 hours) to allow for the administration of antenatal steroids.
- The use of first-line tocolytic treatment with beta-adrenergic agonist therapy, calcium channel blockers or NSAIDs for short-term prolongation of pregnancy (up to 48 hours) to allow for the administration of antenatal steroids.
- Tocolysis is not recommended beyond 34 weeks of gestation and generally not recommended before 24 weeks of gestation but may be considered based on individual circumstances at 23 weeks.
• A single course of corticosteroids is recommended for pregnant women between 24 weeks and 34 weeks of gestation, who are at risk of preterm delivery within 7 days.
• Maintenance therapy with tocolytics is ineffective for preventing preterm birth and improving neonatal outcomes and is not recommended for this purpose.
• Antibiotics should not be used to prolong gestation or improve neonatal outcomes in women with preterm labor and intact membranes.

The Committee on Obstetric Practice and the Society for Maternal-Fetal Medicine (SMFM)
Numerous large clinical studies have evaluated the evidence regarding magnesium sulfate, neuroprotection and preterm births. SMFM recognizes that none of the individual studies found a benefit with regard to their primary outcome. However, the available evidence suggests that magnesium sulfate given before anticipated early preterm birth reduces the risk of cerebral palsy in surviving infants. Physicians electing to use magnesium sulfate for fetal neuroprotection should develop specific guidelines regarding inclusion criteria, treatment regimens, concurrent tocolysis and monitoring in accordance with one of the larger trials (ACOG, 2010; reaffirmed 2015).

Following the FDA’s safety announcement regarding the use of magnesium sulfate to stop preterm labor, ACOG and SMFM released a committee opinion on the use of magnesium sulfate in obstetrics (ACOG, 2016a). The two professional societies continue to support the short-term (usually less than 48 hours) use of magnesium sulfate in obstetric care for appropriate conditions and for appropriate durations of treatment. These conditions include the following:
• Prevention and treatment of seizures in women with preeclampsia or eclampsia
• Fetal neuroprotection before anticipated early preterm (less than 32 weeks of gestation) delivery
• Short-term prolongation of pregnancy (up to 48 hours) to allow for the administration of antenatal corticosteroids in pregnant women between 24 and 34 weeks of gestation who are at risk of preterm delivery within seven days.

U.S. FOOD AND DRUG ADMINISTRATION (FDA)
A February 2011 FDA MedWatch alert issued a warning against use of terbutaline for preterm labor. Terbutaline, given by injection, should not be used in pregnant women for prevention or prolonged treatment (beyond 48-72 hours) of preterm labor. In addition, oral terbutaline should not be used for prevention or any treatment of preterm labor. Serious heart problems and death of the mother may occur. Also, oral terbutaline has not been shown to be effective to prevent or treat preterm labor.

Recommendations:
• Be aware that serious side effects, including maternal heart problems and death, have been reported after lengthy use of terbutaline to manage preterm labor.
• Be aware that there are serious situations where a health care professional may decide that using terbutaline injection for a short time in the hospital may benefit a pregnant woman.
• Oral terbutaline should not be used either to treat preterm labor or prevent repeated preterm labor.
• If you are taking terbutaline for another medical condition (for example, asthma), talk to your healthcare professional if you are pregnant or become pregnant to determine whether terbutaline is still right for you. http://www.fda.gov/forconsumers/consumerupdates/ucm247248.htm#3. Accessed August 2016.
The FDA describes HUAM as a prescription only electronic system (comprising of a tocotransducer, an at-home recorder, a modem and a monitor to receive, process, and display the data) for at-home antepartum measurement of uterine contractions and data transmission by telephone to a clinical setting where it will be displayed. The FDA also states that HUAM is indicated for use, in conjunction with current high-risk care, for the daily at home measurement of uterine activity in pregnancies > 24 weeks of gestation for women with a history of previous preterm birth, to aid in the early detection of preterm labor.

On May 30, 2013, the FDA issued a safety announcement advising health care professionals against using magnesium sulfate injection for more than 5-7 days to stop preterm labor in pregnant women. Administration of magnesium sulfate injection to pregnant women longer than 5-7 days may lead to low calcium levels and bone problems in the developing baby or fetus, including osteopenia and fractures. The shortest duration of treatment that can result in harm to the baby is not known. Magnesium sulfate injection should only be used during pregnancy if clearly needed. If the drug is used during pregnancy, the health care professional should inform the patient of potential harm to the fetus. Additional information available at: http://www.fda.gov/downloads/Drugs/DrugSafety/UCM353335.pdf. Accessed August 2016.

**APPLICABLE CODES**

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Coverage Determination Guidelines may apply.

<table>
<thead>
<tr>
<th>HCPCS Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>J3105</td>
<td>Injection, terbutaline sulfate, up to 1 mg</td>
</tr>
<tr>
<td>J3475</td>
<td>Injection, magnesium sulphate, per 500mg</td>
</tr>
<tr>
<td>S9001</td>
<td>Home uterine monitor with or without associated nursing services</td>
</tr>
<tr>
<td>S9208</td>
<td>Home management of preterm labor, including administrative services, professional pharmacy services, care coordination, and all necessary supplies or equipment (drugs and nursing visits coded separately), per diem (do not use this code with any home infusion per diem code)</td>
</tr>
<tr>
<td>S9349</td>
<td>Home infusion therapy, tocolytic infusion therapy; administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem</td>
</tr>
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**REFERENCES**


The foregoing Health Plan of Nevada/Sierra Health & Life Health Operations protocol has been adopted from an existing UnitedHealthcare coverage determination guideline that was researched, developed and approved by the UnitedHealthcare Coverage Determination Committee.