HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use MACRILEN™ safely and effectively.
See full prescribing information for MACRILEN™.

MACRILEN™ (macimorelin) for oral solution

Initial U.S. Approval: 2017

INDICATIONS AND USAGE
MACRILEN™ is a growth hormone (GH) secretagogue receptor agonist indicated for the diagnosis of adult growth hormone deficiency (1).

Limitations of Use:
The safety and diagnostic performance has not been established for subjects with BMI > 40 kg/m² (1).

DOSAGE AND ADMINISTRATION
• Recommended dose is 0.5 mg/kg as a single oral dose, after fasting for at least 8 hours (2.1).
• See Full Prescribing Information for important preparation and administration instructions (2.3).
• Discontinue therapy with strong CYP3A4 inducers, growth hormones and drugs that affect GH release for an adequate length of time before administering MACRILEN™ (2.2).
• Adequately replace other hormone deficiencies before administering MACRILEN™ (2.2).

DOSAGE FORMS AND STRENGTHS
For oral solution: 60 mg (3)

CONTRAINDICATIONS
None (4)

WARNINGS AND PRECAUTIONS
• QT Prolongation: QT prolongation can lead to development of torsade de pointes-type ventricular tachycardia. Avoid the concomitant use of MACRILEN™ with drugs that are known to prolong QT interval (5.1, 7.1).
• Potential for False Positive Test Results with Use of Strong CYP3A4 Inducers: Discontinue and washout strong CYP3A4 inducers before testing (5.2, 7.2).
• Potential for False Negative Test Results in Recent Onset Hypothalamic Disease: Consider repeat testing if indicated (5.3).

ADVERSE REACTIONS
The most common adverse reactions were dysgeusia, dizziness, headache, fatigue, nausea, hunger, diarrhea, upper respiratory tract infection, feeling hot, hyperhidrosis, nasopharyngitis, and sinus bradycardia (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Novo Nordisk Inc. at 1-800-727-6500, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 11/2019
2.2 Directions for Preparation and Administration

Prepare the MACRILEN™ solution:

a. Weigh the patient in kilograms (i.e., kg).

b. Determine the number of MACRILEN™ pouches needed to prepare the dose:
   i. For a patient weighing up to 120 kg, use 1 pouch.
   ii. For a patient weighing more than 120 kg, use 2 pouches.

c. Use a glass or transparent plastic container with gradations in milliliters (i.e., mL) to dissolve the entire contents of the pouch(es) in the appropriate volume of water.
   i. For 1 pouch dissolve in 120 mL of water (corresponds to 60 mg/120 mL).
   ii. For 2 pouches dissolve in 240 mL of water (corresponds to 120 mg/240 mL).

d. Stir the MACRILEN™ solution gently for about 2 to 3 minutes (a small amount of unsolved particles will remain).

The solution will have a final concentration of 0.5 mg/mL.

e. Use the MACRILEN™ solution within 30 minutes after preparation.

f. Discard any unused MACRILEN™ solution.

Determine the volume of MACRILEN™ solution needed for the test:

g. Determine the recommended dose to be administered by multiplying the patient’s weight in kilograms by 0.5 mg/kg.
   For example, a 70 kg patient will need a 35 mg dose.

h. Determine the volume of prepared MACRILEN™ solution to be administered by dividing the recommended dose by 0.5 mg/mL.
   For example, a patient requiring a dose of 35 mg will need 70 mL of reconstituted MACRILEN™ solution.

2.3 Directions for Preparation and Administration

Prepare and administer by a healthcare professional exactly as follows.

Prepare the MACRILEN™ solution:

1. Have the patient being tested drink the entire volume of MACRILEN™ solution in a drinking glass.
2. Observe the patient being tested per routine for the duration of the test.
3. Draw venous blood samples for GH determination at 30 minutes, 45 minutes, 60 minutes and 90 minutes after administration of MACRILEN™.
4. Prepare serum samples and send to a laboratory for growth hormone determinations.

Table 1: Common Adverse Reactions Reported in at Least Two Individuals Dosed with MACRILEN™ in an Open-Label Study

<table>
<thead>
<tr>
<th>Number of Subjects (n = 154)</th>
<th>Proportion of Subjects (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysgeusia</td>
<td>7</td>
</tr>
<tr>
<td>Dizziness</td>
<td>6</td>
</tr>
<tr>
<td>Headache</td>
<td>6</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6</td>
</tr>
<tr>
<td>Nausea</td>
<td>5</td>
</tr>
<tr>
<td>Hunger</td>
<td>5</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>3</td>
</tr>
<tr>
<td>Feeling hot</td>
<td>2</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>2</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>2</td>
</tr>
</tbody>
</table>

7. Drug Interactions

7.1 Drugs that Prolong QT Interval

Co-administration of MACRILEN™ with drugs that prolong the QT interval (such as antipsychotics, medications that block β1-adrenergic receptors, and electrolyte abnormalities) may lead to development of torsade de pointes-type ventricular tachycardia. Avoid concomitant use of MACRILEN™ with drugs that prolong the QT interval. Sufficient washout time of drugs that are known to prolong the QT interval prior to administration of MACRILEN™ is recommended. [See Dosage and Administration (2.2) and Warnings and Precautions (5.1)].

7.2 Cytochrome P450 (CYP) 3A4 Inducers

Co-administration of a strong CYP3A4 inducer with MACRILEN™ (e.g., carbamazepine, phenytoin, and any other medication known to prolong the QT interval) may lead to false positive test results. Discontinue strong CYP3A4 inducers prior to the use of MACRILEN™. [See Dosage and Administration (2.2) and Warnings and Precautions (5.1)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data with MACRILEN™ use in pregnant women to inform a drug associated risk for adverse developmental outcomes. Animal reproduction studies have not been conducted with MACRILEN™. MACRILEN™ is indicated for the diagnosis of adult growth hormone deficiency. Clinical studies of MACRILEN™ have not been conducted in pregnant women. The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2–4% and 15–20%, respectively.

8.2 Lactation

Risk Summary

There are no data on the presence of macimorelin in human or animal milk, the effects on the breastfed infant or the effects on milk production. The lack of clinical data during lactation precludes a clear determination of the risk of MACRILEN™ to an infant during lactation; therefore, the developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for MACRILEN™ and any potential adverse effects on the breastfed infant from MACRILEN™ or the underlying maternal condition.

8.4 Pediatric Use

The safety and efficacy of MACRILEN™ in pediatric patients have not been established.

8.5 Geriatric Use

Growth hormone secretion normally decreases with age. Therefore, elderly subjects might require a lower cut-off point for diagnosis of adult growth hormone deficiency. Clinical studies of MACRILEN™ did not include a sufficient number of subjects aged 65 and over to determine whether elderly patients respond differently from younger subjects.
10 OVERDOSE
In the event of an overdose, symptomatic and supportive measures should be employed.

11 DESCRIPTION
MACRILEN™ for oral solution is macimorelin acetate, a synthetic growth hormone secretagogue receptor agonist. Macimorelin acetate is described chemically as D-Tryptophanamide, 2-methylalanyl-N-(1R,1’)-formylalanyl)-2(1H-indol-3-yl)-acetate. The molecular formula for macimorelin acetate is C_{26}H_{33}N_{2}O_{5} with a molecular weight of 534.6 g/mol.

![Chemical structure of macimorelin acetate](image)

Each aluminum pouch of MACRILEN™ contains 60 mg of macimorelin, equivalent to 68 mg of macimorelin acetate, and the following inactive ingredients: lactose monohydrate, crospovidone, sodium stearyl fumarate, saccharin sodium and colloidal silicon dioxide.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Macimorelin stimulates GH release by activating growth hormone secretagogue receptors present in the pituitary and hypothalamus.

12.2 Pharmacodynamics
GH stimulation
Maximum GH levels are observed between 30 to 90 minutes after administration of MACRILEN™.

Cardiac electrophysiology
The effects of macimorelin on ECG parameters were investigated in a dedicated THOR study that investigated in a 3-way cross-over design with 60 healthy subjects the effects of a supra-therapeutic dose of macimorelin (2 mg/kg) (4 times the recommended dosage) in comparison with placebo and with moxifloxacin. This study showed a mean baseline- and placebo-adjusted QTcF prolongation of 9.6 milliseconds (11.4 milliseconds) at 4 hours post-dose, which occurred after the maximum macimorelin plasma concentration (0.5 h). A similar increase in the QTcF interval was also observed in a single ascending dose study, which included three dose levels (0.5 mg/kg, 1 mg/kg and 2 mg/kg). All three dose levels showed a similar magnitude of QTcF prolongation in the THOR study, suggesting that QTcF prolongation is an absorption dependent change.

12.3 Pharmacokinetics
The mean plasma macimorelin concentrations are similar between patients with AGHD and healthy subjects for 1.5 hours following administration of a single oral dose of 0.5 mg macimorelin/kg body weight.

Absorption
The maximum plasma macimorelin concentrations (C_{max}) were observed between 0.5 hour and 1.5 hours following oral administration of 0.5 mg macimorelin/kg body weight to patients with AGHD under fasting for at least 8 hours. A liquid meal decreased the macimorelin C_{max} and AUC by 55% and 49%, respectively.

 Elimination
An in vitro human liver microsomes study showed that CYP3A4 is the major enzyme to metabolize macimorelin. Macimorelin was eliminated with a mean terminal half-life (T_{1/2}) of 4.1 hours following administration of a single oral dose of 0.5 mg macimorelin/kg body weight in healthy subjects.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis
Long-term carcinogenesis studies in rodents have not been conducted.

Mutagenesis
Macimorelin did not cause mutations in bacteria under assay conditions with or without metabolic activation. There were also no mutations or clastogenic effects in mouse lymphoma cells with or without metabolic activation.

Impairment of Fertility
No studies have been conducted to assess the effect of macimorelin on fertility.

14 CLINICAL STUDIES
The diagnostic efficacy of the MACRILEN™ test was established in a randomized, open-label, single-dose, cross-over study. The objective of the study was to compare the level of agreement between MACRILEN™ test results and insulin tolerance test (ITT) results in adult patients with different pre-test probability of growth hormone deficiency and healthy control subjects. The four groups of individuals evaluated were:

- **Group A**: Adults with a high likelihood of growth hormone deficiency (GHD)
  - Structural hypothalamic or pituitary lesions and low insulin-like growth factor 1 (IGF-1), and/or
  - Three or more pituitary hormone deficiencies and low IGF-1, or
  - Childhood onset GHD with structural lesions and low IGF-1.
- **Group B**: Adults with an intermediate likelihood of GHD
  - Eligible subjects not qualifying for either high or low likelihood.
- **Group C**: Adults with a low likelihood of GHD
  - One risk factor for GHD only, such as history of distant trauma, or history of pituitary deficits.
- **Group D**: Healthy adults
  - Healthy subjects matching Group A subjects by sex, age ± 5 years, body mass index (BMI) ± 2 kg/m², and estrogen status (females only).

For both the ITT and the MACRILEN™ test, serum concentrations of growth hormone were measured at 30, 45, 60, and 90 minutes after drug administration. The test was considered positive (i.e., growth hormone deficiency diagnosed) if the maximum serum GH level observed after stimulation was less than the pre-specified cut point value of 2.8 ng/ml for the MACRILEN™ test or 5.1 ng/ml for the ITT.

The level of negative and positive agreement between the results of the ITT and the MACRILEN™ test was used to evaluate the performance of the MACRILEN™ test. In the study, the ITT is used as the benchmark (i.e., a negative ITT indicates absence of disease and a positive ITT indicates presence of disease). Negative agreement is the proportion of subjects with a negative ITT (i.e., those who do not have GHD per the ITT) who also have a negative MACRILEN™ test. With a high level of negative agreement, the MACRILEN™ test will not wrongly diagnose an individual without GHD per the ITT as having GHD. Positive agreement is the proportion of subjects with a positive ITT (i.e., those who have GHD per the ITT) who also have a positive MACRILEN™ test. With a high level of positive agreement, the MACRILEN™ test will not wrongly diagnose an individual with GHD per the ITT as not having GHD. The agreement measures are defined mathematically below (see Table 2).

### Table 2: Definition of Agreement between ITT and MACRILEN™

<table>
<thead>
<tr>
<th></th>
<th>Insulin Tolerance Test</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACRILEN™</td>
<td>+</td>
<td>a</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>b</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+b</td>
</tr>
</tbody>
</table>

Total: a+c+d

Positive Agreement (%)=100% x a/(a+c)

Negative Agreement (%)=100% x b/(b+d)

Overall Agreement (%)=100% x (a+d)/(a+b+c+d)

**Results**

One hundred and fifty-seven subjects underwent at least one of the two tests in this study. 59% were male, 41% female, and 86% of white origin. The median age was 41 years (range: 18–66 years) and body mass index 27.5 kg/m² (range: 16–40 kg/m²). The study relied on a cross-over design and each participant was to undergo the two diagnostic tests and serve as his or her own control. Data on both tests were available for 140 subjects (37% in Group A, 37% in Group B, 40% in Group C, and 25% in Group D). One out of 154 MACRILEN™ tests (0.6%) performed failed due to a technical error and 27 out of 157 ITTs (17.2%) performed failed because induction of severe hypoglycemia (i.e., the stimulus) could not be achieved.

Two-by-two tables presenting the pre-specified primary analysis results for the ITT and MACRILEN™ test are shown below for all subjects (Groups A, B, C, and D combined) and for each group separately (see Table 3). The estimates for negative and positive agreement between MACRILEN™ and the ITT in the overall study population were 94% and 74% with lower 95% confidence interval bounds 85% and 63%, respectively. Negative and positive agreement between MACRILEN™ and the ITT in subjects with intermediate or low risk (Groups B and C) were 93% and 61% with lower 95% confidence interval bounds 80% and 43%, respectively. These results are based on peak GH values (maximum GH concentrations across all measurement timepoints).

### Table 3: Diagnostic Outcomes for MACRILEN™ and the ITT in all Subjects (Groups A, B, C, and D) and in Each Group Separately

<table>
<thead>
<tr>
<th></th>
<th>Insulin Tolerance Test</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACRILEN™</td>
<td>+</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>59</td>
</tr>
</tbody>
</table>

Total: 74

Positive Agreement (%)=100% x +/(-/+)

Negative Agreement (%)=100% x -(/+/=/-)

Overall Agreement (%)=100% x (+/+/=/-)

**Groups**

- **Group A**: Adults with a high likelihood of GHD
  - One risk factor for GHD only, such as history of distant trauma or history of pituitary deficits.
- **Group B**: Adults with an intermediate likelihood of GHD
  - Eligible subjects not qualifying for either high or low likelihood.
- **Group C**: Adults with a low likelihood of GHD
  - One risk factor for GHD only, such as history of distant trauma or history of pituitary deficits.
- **Group D**: Healthy adults
  - Healthy subjects matching Group A subjects by sex, age ± 5 years, body mass index (BMI) ± 2 kg/m², and estrogen status (females only).

12.3 Pharmacokinetics
The mean plasma macimorelin concentrations are similar between patients with AGHD and healthy subjects for 1.5 hours following administration of a single oral dose of 0.5 mg macimorelin/kg body weight.

- **Absorption**
  - The maximum plasma macimorelin concentrations (C_{max}) were observed between 0.5 hour and 1.5 hours following oral administration of 0.5 mg macimorelin/kg body weight to patients with AGHD under fasting for at least 8 hours. A liquid meal decreased the macimorelin C_{max} and AUC by 55% and 49%, respectively.

- **Elimination**
  - An in vitro human liver microsomes study showed that CYP3A4 is the major enzyme to metabolize macimorelin. Macimorelin was eliminated with a mean terminal half-life (T_{1/2}) of 4.1 hours following administration of a single oral dose of 0.5 mg macimorelin/kg body weight in healthy subjects.
Repeatability was tested in a subset of 34 subjects who underwent two MACRILEN™ tests. Agreement between the result of the first test and the second test was observed in 31 cases (91.2%).

<table>
<thead>
<tr>
<th>Group C</th>
<th>Insulin Tolerance Test</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>MACRILEN™</td>
<td>+</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>–</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>6</td>
</tr>
</tbody>
</table>

Positive 33%
Negative 94%
Overall 85%

<table>
<thead>
<tr>
<th>Group D</th>
<th>Insulin Tolerance Test</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>MACRILEN™</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

Positive 0%
Negative 96%
Overall 92%

16 HOW SUPPLIED/STORAGE AND HANDLING
MACRILEN™ 60 mg is supplied as white to off-white granules in an aluminum pouch. Each pouch contains 60 mg macimorelin (equivalent to 68 mg macimorelin acetate) that when reconstituted with 120 mL of water provides a 60 mg/120 mL (0.5 mg/mL) macimorelin solution.

MACRILEN™ is available in boxes containing 1 pouch per box (NDC 0169-1401-01).

Before administration, MACRILEN™ for oral solution must be reconstituted by a healthcare professional [see Dosage and Administration (2.3)].

Store pouches under refrigeration at 2-8°C (36-46°F).

The solution must be used within 30 minutes after preparation. Discard unused portion.

17 PATIENT COUNSELING INFORMATION
Instruct patients to discontinue treatment with GH at least one week before administering MACRILEN™. Also, instruct patients to discontinue other medications that may interfere with the diagnostic test results prior to MACRILEN™ administration [see Drug Interactions (7.2, 7.3)].

Instruct patients to fast for at least 8 hours before MACRILEN™ administration [see Dosage and Administration (2.2)].