The effect of semaglutide on cardiac repolarization was tested in a thorough QTc trial. Semaglutide did not prolong QTc intervals at doses up to 1.5 mg at steady state.

- Clinical efficacy and safety - Summary from Phase III clinical trial in chronic weight management conducted by Zydus Lifesciences Limited

A Multicenter, Randomized, Comparative, Active-Controlled, Open label, Phase 3 Study to Evaluate the Efficacy and Safety of Semaglutide Injection in Comparison with Reference Biologic in Obesity Management. Test product was Semaglutide Injection 15 mg/3 mL (5 mg/mL) manufactured by M/s. Zydus Lifesciences Limited and Comparator Product was Reference Biologic Injection (Semaglutide) (0.25 mg / 0.5 mg / 1 mg / 1.7 mg / 2.4 mg) pre-filled pen - (All manufactured by Novo Nordisk).

This study was conducted in male and female patients aged 18 to 75 years (both inclusive) who were overweight or obese, defined by a body mass index (BMI) ≥ 30 kg/m², or ≥ 27 kg/m² with at least one weight-related comorbidity (treated or untreated) such as hypertension, dyslipidaemia, or type 2 diabetes mellitus (T2DM).

For patients with type 2 diabetes mellitus participating in this study, additional criteria applied. These patients were required to have glycosylated haemoglobin (HbA1c) between 7.0% and 10.0% (both inclusive) at the time of screening, have a confirmed diagnosis of T2DM for at least 180 days prior to screening, and be receiving a stable treatment regimen consisting of up to three oral glucose-lowering agents (Metformin, sulfonylureas, SGLT2 inhibitors, or thiazolidinediones) for a minimum of 90 days prior to screening visit, along with diet and exercise measures.

A total of 313 patients were screened, and 282 patients were randomized using a computer generated randomization program for 24 weeks (168±3 days) treatment of either of the two study arms i.e., Semaglutide Injection 15 mg/3 mL (5 mg/mL) (Test Product) or Reference Biologic Injection (Semaglutide) (0.25 mg / 0.5 mg / 1 mg / 1.7 mg / 2.4 mg) pre-filled pen (Comparator Product) in 2:1 proportion. Total patients randomized were 188 in Semaglutide Injection 15 mg/3 mL (5 mg/mL) (Test Product) and 94 in Reference Biologic Injection (Semaglutide) (0.25 mg / 0.5 mg / 1 mg / 1.7 mg / 2.4 mg) pre-filled pen (Comparator Product).

All enrolled patients received once-weekly subcutaneous Semaglutide (Test or Comparator) for a total treatment duration of 24 weeks. Dose escalation followed a fixed titration schedule to improve tolerability: Week 0: All patients received the initial dose of 0.25 mg once weekly for 4 weeks. Week 4: All patients were up titrated to the dosage of 0.5 mg once weekly. Week 8: All patients were up titrated to the dosage of 1 mg once weekly. Week 12: All patients were up titrated to the dosage of 1.7 mg once weekly. Week 16: All patients were up titrated to the dosage of 2.4 mg once weekly. Week 16 to week 24: All patients were on maintenance dose of 2.4 mg once weekly. Patients unable to tolerate the recommended maintenance dose (2.4 mg once weekly) were permitted to down titrate to 1.7 mg once weekly.

The primary efficacy endpoint was the Percentage change in body weight from baseline to week 24. In the PP analysis population, the least square mean (LSM) percentage change in body weight from baseline to Week 24 was −11.78% and −12.11%, respectively, with an LSM difference of 0.330 (95% CI: −0.66, 1.32; p = 0.5132). The 95% confidence intervals for the between-group difference were well within the pre-specified non-inferiority margin of 5 percentage points defined in the protocol, confirming non-inferiority of the Test Product versus the Comparator Product for the primary endpoint. These results were consistent with those of the mITT analysis, confirming the robustness of non-inferiority.

**Table 7: Percentage change in body weight from baseline to week 24.**

| Visit | Statistics | Test Product (N = 171) | Comparator Product (N = 85) |
|---|---|---|---|
| Visit 1 / Baseline | Mean (SD) | **86.81 (13.64)** | **89.09 (17.06)** |
| | Median | 84.60 | 86.80 |
| | (Min, Max) | (65.00, 144.60) | (65.00, 179.00) |
| Visit 8 / Week 24 | Mean (SD) | **76.59 (12.97)** | **78.25 (15.28)** |
| | Median | 74.00 | 75.40 |
| | (Min, Max) | (46.30, 130.00) | (53.10, 148.00) |
| Percentage change from baseline to Visit 8 / Week 24 | LSM (SE) | **-11.7752 (0.2909)** | **-12.1054 (0.4126)** |
| | LS mean difference | **0.3301** | |
| | 95% CI of LS mean difference | (-0.66, 1.32) | |
| | ***P*-value** | **0.5132** | |

The secondary efficacy endpoints were consistent with the primary result and further support comparable efficacy between the two treatments. The percentage change in body weight from baseline to Weeks 4, 8, 12, 16 and 20 showed progressive and clinically meaningful weight reduction in both treatment groups, with similar LSM reductions at each visit and small between-group differences. Responder analyses demonstrated that the proportions of patients achieving ≥5% and ≥10% reductions in body weight from baseline increased over time in both groups up to Week 24, with high responder rates and no clinically meaningful differences between the Test and Comparator products.

In the diabetic subgroup, both treatments were associated with marked improvements in glycaemic control. HbA1c decreased from a mean baseline of about 8.3% to approximately 6.6 to 6.8% at Week 24 in both groups respectively, with an LSM change from baseline of −1.52% for the Test Product and −1.80% for the Comparator Product; the between-group LSM difference (0.27%; 95% CI: −0.14, 0.68; p = 0.1953) was not statistically significant and not clinically meaningful

Overall, across the primary and secondary efficacy endpoints including body weight, responder status (≥5% and ≥10% weight loss), BMI, waist circumference, SF-36 physical functioning, and glycaemic parameters in diabetic and non-diabetic patients - the Test Product demonstrated efficacy closely comparable to the Comparator Product, and the predefined criterion for non-inferiority on the primary endpoint was clearly met.

In terms of safety evaluation, a total of 458 adverse events were reported in 178 patients. 318 adverse events were reported in test product arm and 140 adverse events were reported in comparator product arm considering 2:1 proportion. No serious adverse events were reported during the study. There were no clinically significant changes observed in clinical laboratory parameters, vital signs (including pulse rate, respiratory rate, body temperature, systolic and diastolic blood pressure), systemic examination findings, retinal examination (fundoscopy) observations, 12-lead electrocardiogram results, or routine urinalysis in either treatment group throughout the study period.

**5.3 Pharmacokinetic properties**

**Absorption**

Absolute bioavailability of semaglutide is 89%. Maximum concentration of semaglutide is reached 1 to 3 days post dose. Similar exposure is achieved with subcutaneous administration of semaglutide in the abdomen, thigh, or upper arm.

In patients with type 2 diabetes, semaglutide exposure increases in a dose-proportional manner for once-weekly doses of 0.5 mg, 1 mg and 2 mg. Steady-state exposure is achieved following 4-5 weeks of once-weekly administration. In patients with type 2 diabetes, the mean population-PK estimated steady-state concentrations following once weekly subcutaneous administration of 0.5 mg and 1 mg semaglutide were approximately 65.0 ng/mL and 123.0 ng/mL, respectively. In the trial comparing semaglutide 1 mg and 2 mg, the mean steady state concentrations were 111.1 ng/mL and 222.1 ng/mL, respectively. The average semaglutide steady state concentration following subcutaneous administration of SEMAGLUTIDE was approximately 75 nmol/L in patients with either obesity (BMI greater than or equal to 30 kg/m²) or overweight (BMI greater than or equal to 27 kg/m²). The steady state exposure of SEMAGLUTIDE increased proportionally with doses up to 2.4 mg once-weekly.

**Distribution**

The mean apparent volume of distribution of semaglutide following subcutaneous administration in patients with type 2 diabetes is approximately 12.5L. Semaglutide is extensively bound to plasma albumin (>99%) which results in decreased renal clearance and protection from degradation.

**Elimination**

The apparent clearance of semaglutide in patients with type 2 diabetes, obesity or overweight is approximately 0.05 L/h. With an elimination half-life of approximately 1 week, semaglutide will be present in the circulation for about 5 weeks after the last dose. In obesity or overweight patients, it will be present in the circulation for about 5 to 7 weeks after the last dose of 2.4 mg.

**Metabolism**

The primary route of elimination for semaglutide is metabolism following proteolytic cleavage of the peptide backbone and sequential beta-oxidation of the fatty acid sidechain.

**Excretion**

The primary excretion routes of semaglutide-related material are via the urine and feces.

Approximately 3% of the dose is excreted in the urine as intact semaglutide.

**Patients with Renal impairment**

Renal impairment does not impact the pharmacokinetics of semaglutide in a clinically relevant manner. This was shown in a study with a single dose of 0.5 mg semaglutide in patients with different degrees of renal impairment (mild, moderate, severe, ESRD) compared with subjects with normal renal function.

The pharmacokinetics were also assessed in subjects with overweight (BMI 27-29.9 kg/m²) or obesity (BMI greater than or equal to 30 kg/m²) and mild to moderate renal impairment, based on data from clinical trials.

**Patients with Hepatic impairment**

Hepatic impairment does not have any impact on the exposure of semaglutide. The pharmacokinetics of semaglutide were evaluated in patients with different degrees of hepatic impairment (mild, moderate, severe) compared with subjects with normal hepatic function in a study with a single-dose of 0.5 mg semaglutide.

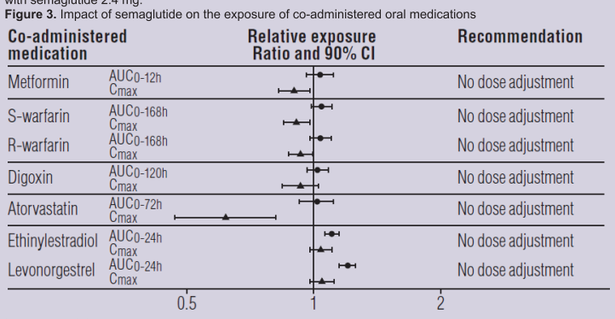
**Drug Interaction Studies**

In vitro studies have shown very low potential for semaglutide to inhibit or induce CYP enzymes, and
to inhibit drug transporters.

The delay of gastric emptying with semaglutide may influence the absorption of concomitantly
administered oral medicinal products. The potential effect of semaglutide on the absorption of co-administered oral medications was studied in trials at semaglutide 1 mg steady-state exposure.

No clinically relevant drug-drug interaction with semaglutide was observed based on
the evaluated medications (figure 3); therefore, no dose adjustment is required when co-administered with semaglutide. In a separate study, no apparent effect on the rate of gastric emptying was observed
with semaglutide 2.4 mg.

**Figure 3.** Impact of semaglutide on the exposure of co-administered oral medications




**Immunogenicity**

**T2DM:**

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies (ADAs) in the studies described below with the incidence of ADAs in other studies, including those of semaglutide or of other semaglutide products.

Across the placebo- and active-controlled glycemic control trials, 32 out of 3,150 (1%) SEMBOLIC treated patients developed ADAs to the active ingredient. Of the 32 semaglutide-treated patients that developed semaglutide ADAs, 19 patients (0.6% of the overall population) developed antibodies cross-reacting with native GLP-1. The in vitro neutralizing activity of the antibodies is uncertain at this time.

**CHRONIC WEIGHT MANAGEMENT**:

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those of semaglutide or of other semaglutide products.

During the 68-week treatment periods in Studies 1 and 2, 50/1709 (3%) of SEMBOLIC-treated patients developed anti-semaglutide antibodies. Of these 50 SEMBOLIC-treated patients, 28 patients (2% of the total SEMBOLIC-treated study population) developed antibodies that cross-reacted with native GLP-1. No identified clinically significant effect of anti-semaglutide antibodies on pharmacokinetics for SEMBOLIC was observed. There is insufficient evidence to characterize the effects of anti-semaglutide antibodies on pharmacodynamics or effectiveness of semaglutide.

**6. Nonclinical properties**

**6.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

In a 2-year carcinogenicity study in CD-1 mice, subcutaneous doses of 0.3, 1 and 3 mg/kg/day [2-, 11-, and 30-fold the maximum recommended human dose (MRHD) of 2 mg/week, based on AUC] were administered to the males, and 0.1, 0.3 and 1 mg/kg/day (1-, 2-, and 7-fold MRHD) were administered to the females. A statistically significant increase in thyroid C-cell adenomas and a numerical increase in C-cell carcinomas were observed in males and females at clinically relevant exposures.

In a 2-year carcinogenicity study in Sprague Dawley rats, subcutaneous doses of 0.0025, 0.01, 0.025 and 0.1 mg/kg/day were administered (below quantification, 0.2-, 0.5-, and 3-fold the exposure at the MRHD). A statistically significant increase in thyroid C-cell adenomas was observed in males and females at all dose levels, and a statistically significant increase in thyroid C-cell carcinomas was observed in males at ≥0.01 mg/kg/day, at clinically relevant exposures.

Human relevance of thyroid C-cell tumors in rats is unknown and could not be determined by clinical studies or nonclinical studies.

Semaglutide was not mutagenic or clastogenic in a standard battery of genotoxicity tests (bacterial mutagenicity (Ames), human lymphocyte chromosome aberration, rat bone marrow micronucleus).

In a combined fertility and embryo-fetal development study in rats, subcutaneous doses of 0.01, 0.03 and 0.09 mg/kg/day (0.06-, 0.2-, and 0.6-fold the MRHD) were administered to male and female rats. Males were dosed for 4 weeks prior to mating, and females were dosed for 2 weeks prior to mating and throughout organogenesis until Gestation Day 17. No effects were observed on male fertility. In females, an increase in estrus cycle length was observed at all dose levels, together with a small reduction in numbers of corpora lutea at ≥0.03 mg/kg/day. These effects were likely an adaptive response secondary to the pharmacological effect of semaglutide on food consumption and body weight.

**7. Description**

SEMBOLIC (semaglutide) injection, for subcutaneous use, contains semaglutide, a human GLP-1 receptor agonist (or GLP-1 analog). The peptide backbone is produced by synthetic route. The main protraction mechanism of semaglutide is albumin binding, facilitated by modification of position 26 lysine with a hydrophilic spacer and a C18 fatty di-acid. Furthermore, semaglutide is modified in position 8 to provide stabilization against degradation by the enzyme dipeptidyl-peptidase 4 (DPP-4). A minor modification was made in position 34 to ensure the attachment of only one fatty di-acid. The molecular formula is $C_{187}H_{291}N_{45}O_{59}$ and the molecular weight is 4113.58 g/mol.

**8. Pharmaceutical particulars**

**8.1 Incompatibilities**

Semaglutide injection should not be mixed with any other medicine.

**8.2 Shelf-life**

18 months

**8.3 Packaging information**

Semaglutide injection is supplied as a multiple dose cartridge containing a clear colorless solution of 5 mg/mL.
Cartridge: Semaglutide Injection is filled in Type I glass cartridge.
Semaglutide Injection is presented with the following pack configuration −
Cartridge:

| Sr. No. | Pack size |
|---|---|
| 1 | Pack of 1 x 3 mL cartridge of Semaglutide Injection along with 10 ultrafine needles in a single pack. |

Pen Device:

| Sr. No. | Pack size |
|---|---|
| 1 | Pack of one reusable customized pen for Semaglutide Injection in a single pack. |

**8.4 Storage and handing instructions**

Store in a refrigerator (2°C to 8°C). Do not freeze.

After first use, store the assembled pen for 56 days at controlled room temperature (15°C to 30°C) or in a refrigerator (2°C to 8°C) for 8 months. Protect from excessive heat and sunlight.

Keep out of reach of children. Always remove and safely discard the needle after each injection and store the pen without an injection needle attached. Always use a new needle for each injection.

Use Reusable **Customized Pen and supplied needle for Semaglutide Injection 15mg/3mL (5mg/mL).**

**9. Details of manufacturer**

Zydus Lifesciences Limited
Plot Survey No. 23, 25/P, 37, 40/P, 42 to 47, Sarkhej- Bavla N.H.No. 8A, Opp. Ramdev Masala,
Village: Changodar, Tal: Sanand, Dist.-Ahmedabad - 382213.

**10. Details of permission or licence number with date**

MF/SND/26/000004 and MF/SND/26/000006 dated 15/01/2026

**11. Date of revision**

Not applicable

TORRENT PHARMA
Marketed by :
**TORRENT PHARMACEUTICALS LTD.**
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To report adverse events, please visit
www.torrentpharma.com

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XXXXXXX -9093

*To be sold by retail on the prescription of endocrinologist or internal medicine specialists only*

**WARNING: RISK OF THYROID C-CELL TUMORS**
***See full prescribing information for complete boxed warning***

- **In rodents, semaglutide causes thyroid C-cell tumors at clinically relevant exposures. It is unknown whether semaglutide causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as the human relevance of semaglutide-induced rodent thyroid C-cell tumors has not been determined.**
- **Semaglutide is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk of MTC and symptoms of thyroid tumors.**

**1. Generic Name**

# Semaglutide Injection 15mg/3mL

**Sembolic™**

**2. Qualitative and quantitative composition**

Each mL contains:

| | |
|---|---|
| Semaglutide | 5 mg |
| Phenol I.P. | 4.5 mg |
| Water for Injections I.P. | q.s. |

Semaglutide is synthetic in origin.
Semaglutide Injection is a sterile, aqueous, clear, colorless solution. Semaglutide Injection has a pH of approximately 7.4.

**3. Dosage form and strength**

Injection
Dosage strength: 15mg/3mL (5mg/mL)

**4. Clinical particulars**

**4.1 Therapeutic indication**

**T2DM**:

SEMBOLIC is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise

- As monotherapy, when metformin is considered inappropriate due to intolerance or contraindications.
- In addition to other medicinal products for the treatment of diabetes.

Limitations of Use:

- Has not been studied in patients with a history of pancreatitis. Consider another antidiabetic therapy
- Not for treatment of type 1 diabetes mellitus

**CHRONIC WEIGHT MANAGEMENT:**

SEMBOLIC is indicated as an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of

- 30 kg/m² or greater (obesity) or
- 27 kg/m² or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, type 2 diabetes mellitus, or dyslipidemia).

Limitations of Use:

- SEMBOLIC should not be used in combination with other semaglutide-containing products or any other GLP-1 receptor agonist.
- The safety and efficacy of coadministration with other products for weight loss have not been established.
- SEMBOLIC has not been studied in patients with a history of pancreatitis.

**4.2 Posology and method of administration**

**T2DM:**

**Important Administration Instructions**

- Inspect SEMBOLIC visually before use. It should appear clear and colorless. Do not use SEMBOLIC if particulate matter and coloration is seen.
- Administer SEMBOLIC once weekly, on the same day each week, at any time of the day, with or without meals.
- Inject SEMBOLIC subcutaneously to the abdomen, thigh, or upper arm. Instruct patients to use a different injection site each week when injecting in the same body region.
- When using SEMBOLIC with insulin, instruct patients to administer as separate injections and to never mix the products. It is acceptable to inject SEMBOLIC and insulin in the same body region, but the injections should not be adjacent to each other.

**Recommended Dosage**

- Initiate SEMBOLIC with a dosage of 0.25 mg injected subcutaneously once weekly for 4 weeks. The 0.25 mg dosage is intended for treatment initiation and is not effective for glycemic control.
- After 4 weeks on the 0.25 mg dosage, increase the dosage to 0.5 mg once weekly.
- If additional glycemic control is needed after at least 4 weeks on the 0.5 mg dosage, the dosage may be increased to 1 mg once weekly.
- If additional glycemic control is needed after at least 4 weeks on the 1 mg dosage, the dosage may be increased to 2 mg once weekly. The maximum recommended dosage is 2 mg once weekly.
- The day of weekly administration can be changed if necessary as long as the time between two doses is at least 2 days (>48 hours).
- If a dose is missed, administer SEMBOLIC as soon as possible within 5 days after the missed dose. If more than 5 days have passed, skip the missed dose and administer the next dose on the regularly scheduled day. In each case, patients can then resume their regular once weekly dosing schedule.

| | Dose | Delivered volume | Dose regimen |
|---|---|---|---|
| **Type 2 Diabetes Mellitus** | 0.25 mg | 0.05 mL | Escalation doses |
| | 0.5 mg | 0.10 mL | |
| | 1 mg | 0.20 mL | |
| | 2 mg | 0.40 mL | Maintenance dose |

**CHRONIC WEIGHT MANAGEMENT:**

Select adult patients for SEMBOLIC treatment as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management based on their BMI.

**Table 1** presents a chart for determining BMI based on height and weight. BMI is calculated by dividing weight (in kilograms) by height (in meters) squared.

| Weight | (lb) | 125 | 130 | 135 | 140 | 145 | 150 | 155 | 160 | 165 | 170 | 175 | 180 | 185 | 190 | 195 | 200 | 205 | 210 | 215 | 220 | 225 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | (kg) | 56.8 | 59.1 | 61.4 | 63.6 | 65.9 | 68.2 | 70.5 | 72.7 | 75.0 | 77.3 | 79.5 | 81.8 | 84.1 | 86.4 | 88.6 | 90.9 | 93.2 | 95.5 | 97.7 | 100.0 | 102.3 |
| Height (in) | (cm) | | | | | | | | | | | | | | | | | | | | | |
| 58 | 147.3 | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 34 | 35 | 36 | 37 | 38 | 39 | 40 | 41 | 42 | 43 | 44 | 45 | 46 | 47 |
| 59 | 149.9 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 | 41 | 43 | 44 | 45 | 46 |
| 60 | 152.4 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 | 41 | 42 | 43 | 44 |
| 61 | 154.9 | 24 | 25 | 26 | 27 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 | 41 | 42 | 43 |
| 62 | 157.5 | 23 | 24 | 25 | 26 | 27 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 38 | 39 | 40 | 41 |
| 63 | 160.0 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 36 | 37 | 38 | 39 | 40 |
| 64 | 162.6 | 22 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 34 | 35 | 36 | 37 | 38 | 39 |
| 65 | 165.1 | 21 | 22 | 23 | 23 | 24 | 25 | 26 | 27 | 28 | 28 | 29 | 30 | 31 | 32 | 33 | 33 | 34 | 35 | 36 | 37 | 38 |
| 66 | 167.6 | 20 | 21 | 22 | 23 | 23 | 24 | 25 | 26 | 27 | 27 | 28 | 29 | 30 | 31 | 32 | 32 | 33 | 34 | 35 | 36 | 36 |
| 67 | 170.2 | 20 | 20 | 21 | 22 | 23 | 24 | 24 | 25 | 26 | 27 | 27 | 28 | 29 | 30 | 31 | 31 | 32 | 33 | 34 | 35 | 35 |
| 68 | 172.7 | 19 | 20 | 21 | 21 | 22 | 23 | 24 | 24 | 25 | 26 | 27 | 27 | 28 | 29 | 30 | 30 | 31 | 32 | 33 | 34 | 34 |
| 69 | 175.3 | 18 | 19 | 20 | 21 | 21 | 22 | 23 | 24 | 24 | 25 | 26 | 27 | 27 | 28 | 29 | 30 | 30 | 31 | 32 | 33 | 33 |
| 70 | 177.8 | 18 | 19 | 19 | 20 | 21 | 22 | 22 | 23 | 24 | 24 | 25 | 26 | 27 | 27 | 28 | 29 | 29 | 30 | 31 | 32 | 32 |
| 71 | 180.3 | 17 | 18 | 19 | 20 | 20 | 21 | 22 | 22 | 23 | 24 | 24 | 25 | 26 | 27 | 27 | 28 | 29 | 29 | 30 | 31 | 31 |
| 72 | 182.9 | 17 | 18 | 18 | 19 | 20 | 20 | 21 | 22 | 22 | 23 | 24 | 24 | 25 | 26 | 27 | 27 | 28 | 29 | 29 | 30 | 31 |
| 73 | 185.4 | 17 | 17 | 18 | 19 | 19 | 20 | 20 | 21 | 22 | 22 | 23 | 24 | 24 | 25 | 26 | 26 | 27 | 28 | 28 | 29 | 30 |
| 74 | 188.0 | 16 | 17 | 17 | 18 | 19 | 19 | 20 | 21 | 21 | 22 | 23 | 23 | 24 | 24 | 25 | 26 | 26 | 27 | 28 | 28 | 29 |
| 75 | 190.5 | 16 | 16 | 17 | 18 | 18 | 19 | 19 | 20 | 21 | 21 | 22 | 23 | 23 | 24 | 24 | 25 | 26 | 26 | 27 | 28 | 28 |
| 76 | 193.0 | 15 | 16 | 16 | 17 | 18 | 18 | 19 | 20 | 20 | 21 | 21 | 22 | 23 | 23 | 24 | 24 | 25 | 26 | 26 | 27 | 27 |

**Important Administration Instructions**

- In patients with type 2 diabetes, monitor blood glucose prior to starting SEMBOLIC and during SEMBOLIC treatment.
- Prior to initiation of SEMBOLIC, train patients on proper injection technique.
- Inspect SEMBOLIC visually prior to each injection. Only use if solution is clear, colorless, and contains no particles.
- Administer SEMBOLIC once weekly, on the same day each week, at any time of day, with or without meals.
- Inject SEMBOLIC subcutaneously in the abdomen, thigh, or upper arm. The time of day and the injection site can be changed without dose adjustment.

**Recommended Dosage**

**Dosage Initiation and Escalation**

- Initiate SEMBOLIC with a dosage of 0.25 mg injected subcutaneously once-weekly. Then follow the dose escalation schedule presented in Table 2 to minimize gastrointestinal adverse reactions.
- If patients do not tolerate a dose during dosage escalation, consider delaying dosage escalation for 4 weeks.
- The 0.25 mg, 0.5 mg, and 1 mg once-weekly dosages are initiation and escalation dosages and are not approved as maintenance dosages for chronic weight management.

**Table 2 -** Recommended Dosage Regimen for Adults

| Treatment | Weeks | Once weekly Subcutaneous Dosage |
|---|---|---|
| Initiation | 1 through 4 | 0.25 mg[a] |
| Escalation | 5 through 8 | 0.5 mg[a] |
| | 9 through 12 | 1 mg[a] |
| | 13 through 16 | 1.7 mg |
| Maintenance | 17 and onward | 1.7 mg or 2.4 mg |

[a]Dosage not approved as maintenance for chronic weight management.

| | Dose | Delivered volume | Dose regimen |
|---|---|---|---|
| **Chronic weight management** | 0.25 mg | 0.05 mL | Escalation doses |
| | 0.5 mg | 0.10 mL | |
| | 1 mg | 0.20 mL | |
| | 1.7 mg | 0.34 mL | |
| | 2.4 mg | 0.48 mL | Maintenance dose |

**Maintenance Dosage**

- The maintenance dosage of SEMBOLIC in adults is either 2.4 mg (recommended) or 1.7 mg once weekly.
- Consider treatment response and tolerability when selecting the maintenance dosage.

**Dosage Modifications for Adverse Reactions**

- If patients do not tolerate the 2.4 mg once-weekly maintenance dosage, the maintenance dosage may be reduced to 1.7 mg once-weekly.
- Discontinue SEMBOLIC if the patient cannot tolerate the 1.7 mg once-weekly dosage.

**Recommendations Regarding Missed Dose**

- If one dose is missed and the next scheduled dose is more than 2 days away (48 hours), administer SEMBOLIC as soon as possible. If one dose is missed and the next scheduled dose is less than 2 days away (48 hours), do not administer the dose. Resume dosing on the regularly scheduled day of the week.
- If 2 or more consecutive doses are missed, resume dosing as scheduled or, if needed, reinitiate SEMBOLIC and follow the dose escalation schedule, which may reduce the occurrence of gastrointestinal symptoms associated with reinitiation of treatment.

**4.3 Contraindications**

- A personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2)
- A serious hypersensitivity reaction to semaglutide or to any of the excipients in SEMBOLIC. Serious hypersensitivity reactions including anaphylaxis and angioedema have been reported with SEMBOLIC

**4.4 Special warnings and precautions for use**

**Risk of Thyroid C-Cell Tumors**

- In mice and rats, semaglutide caused a dose-dependent and treatment-duration-dependent increase in the incidence of thyroid C-cell tumors (adenomas and carcinomas) after lifetime exposure at clinically relevant plasma exposures. It is unknown whether SEMBOLIC causes thyroid C-cell tumors, including MTC, in humans as human relevance of semaglutide-induced rodent thyroid C-cell tumors has not been determined.
- Cases of MTC in patients treated with liraglutide, another GLP-1 receptor agonist, have been reported in the postmarketing period; the data in these reports are insufficient to establish or exclude a causal relationship between MTC and GLP-1 receptor agonist use in humans.
- SEMBOLIC is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2. Counsel patients regarding the potential risk for MTC with the use of SEMBOLIC and inform them of symptoms of thyroid tumors (e.g., a mass in the neck, dysphagia, dyspnea, persistent hoarseness).
- Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with SEMBOLIC. Such monitoring may increase the risk of unnecessary procedures, due to the low test specificity for serum calcitonin and a high background incidence of thyroid disease. Significantly elevated serum calcitonin value may indicate MTC and patients with MTC usually have calcitonin values >50 ng/L. If serum calcitonin is measured and found to be elevated, the patient should be further evaluated. Patients with thyroid nodules noted on physical examination or neck imaging should also be further evaluated.

**Pancreatitis**

- In glycemic control trials, acute pancreatitis was confirmed by adjudication in 7 SEMBOLIC-treated patients (0.3 cases per 100 patient years) versus 3 in comparator-treated patients (0.2 cases per 100 patient years). One case of chronic pancreatitis was confirmed in an SEMBOLIC-treated patient. In a 2-year trial, acute pancreatitis was confirmed by adjudication in 8 SEMBOLIC-treated patients (0.27 cases per 100 patient years) and 10 placebo-treated patients (0.33 cases per 100 patient years), both on a background of standard of care.
- After initiation of SEMBOLIC, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back and which may or may not be accompanied by vomiting). If pancreatitis is suspected, SEMBOLIC should be discontinued and appropriate management initiated; if confirmed, SEMBOLIC should not be restarted.
- SEMBOLIC has not been studied in patients with a history of pancreatitis. It is unknown if patients with a history of pancreatitis are at higher risk for development of pancreatitis on SEMBOLIC.

**Diabetic Retinopathy Complications**

- In a trial of adult patients with type 2 diabetes and BMI greater than or equal to 27 kg/m², diabetic retinopathy was reported by 4.0% of SEMBOLIC-treated patients and 2.7% placebo-treated patients.
- In a 2-year trial involving patients with type 2 diabetes and high cardiovascular risk, more events of diabetic retinopathy complications occurred in patients treated with SEMBOLIC (3.0%) compared to placebo (1.8%). The absolute risk increase for diabetic retinopathy complications was larger among patients with a history of diabetic retinopathy at baseline (SEMBOLIC 8.2%, placebo 5.2%) than among patients without a known history of diabetic retinopathy (SEMBOLIC 0.7%, placebo 0.4%).
- Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy. The effect of long-term glycemic control with SEMBOLIC on diabetic retinopathy complications has not been studied. Patients with a history of diabetic retinopathy should be monitored for progression of diabetic retinopathy.

**Never Share an SEMBOLIC Pen Between Patients**

- SEMBOLIC pens must never be shared between patients, even if the needle is changed. Pen-sharing poses a risk for transmission of blood-borne pathogens.

**Hypoglycemia**

- SEMBOLIC lowers blood glucose and can cause hypoglycemia. In a trial of adult patients with type 2 diabetes and BMI greater than or equal to 27 kg/m², hypoglycemia (defined as a plasma glucose less than 54 mg/dL) was reported in 6.2% of SEMBOLIC-treated patients versus 2.5% of placebo-treated patients. One episode of severe hypoglycemia (requiring the assistance of another person) was reported in one SEMBOLIC-treated patient versus no placebo-treated patients. Patients with type 2 diabetes mellitus taking SEMBOLIC in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin may have an increased risk of hypoglycemia, including severe hypoglycemia.
- Hypoglycemia has been observed in patients treated with semaglutide at doses of 0.5 and 1 mg in combination with insulin. The addition of SEMBOLIC in patients treated with insulin has not been evaluated. Inform patients of the risk of hypoglycemia and educate them on the signs and symptoms of hypoglycemia.
- In patients with type 2 diabetes, monitor blood glucose prior to starting SEMBOLIC and during SEMBOLIC treatment. When initiating SEMBOLIC, consider reducing the dose of concomitantly administered insulin secretagogue (such as sulfonylureas) or insulin to reduce the risk of hypoglycemia.

**Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin**

| | | | | | | |
|---|---|---|---|---|---|---|
| **PRODUCT NAME :** | SEMBOLIC Inj. | **COUNTRY :** Domestic P2P | **LOCATION :** Zydus Life. | | **SUPERSEDES A/W NO. :** | |
| **ITEM / PACK :** | Insert_ | **NO. OF COLORS : 4** | **SUBSTRATE :** | | | |
| **DESIGN STYLE :** | Front | **PANTONE SHADE Nos. :** | **REMARK :** | | | |
| **CODE :** | XXXXXXX -9093 | **CMYK** | **Activities** | **Department** | **Name** | **Signature** | **Date** |
| **DIMENSION (MM) :** | S/S | | **Prepared By** | **Pkg.Dev** | | | |
| **ART WORK SIZE :** | 230 x 560 mm | | **Reviewed By** | **Pkg.Dev** | | | |
| **DATE :** | 12-02-2026 | | **Reviewed By** | **CR** | | | |
| | | | **Approved By** | **Quality** | | | |
| | | | **Approved By** | **Quality** | | | |

**This colour proof is not colour binding. Follow pantone shade reference for actual colour matching.**

- Patients receiving SEMBOLIC in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin may have an increased risk of hypoglycemia, including severe hypoglycemia. The risk of hypoglycemia may be lowered by a reduction in the dose of sulfonylurea (or other concomitantly administered insulin secretagogue) or insulin. Inform patients using these concomitant medications of the risk of hypoglycemia and educate them on the signs and symptoms of hypoglycemia.

**Acute Kidney Injury**

- There have been postmarketing reports of acute kidney injury and worsening of chronic renal failure, which may sometimes require hemodialysis, in patients treated with GLP-1 receptor agonists. Patients with renal impairment may be at greater risk of acute kidney injury, but some of these events have been reported in patients without known underlying renal disease. Majority of the reported events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration. Monitor renal function when initiating or escalating doses of SEMBOLIC in patients reporting severe adverse gastrointestinal reactions.

**Hypersensitivity**

- Serious hypersensitivity reactions (e.g., anaphylaxis, angioedema) have been reported in patients treated with SEMBOLIC. If hypersensitivity reactions occur, discontinue use of SEMBOLIC; treat promptly per standard of care, and monitor until signs and symptoms resolve. Do not use in patients with a previous hypersensitivity to SEMBOLIC.
  Anaphylaxis and angioedema have been reported with other GLP-1 receptor agonists. Use caution in a patient with a history of angioedema or anaphylaxis with another GLP-1 receptor agonist because it is unknown whether such patients will be predisposed to anaphylaxis with SEMBOLIC.

**Acute Gallbladder Disease**

- Acute events of gallbladder disease such as cholelithiasis or cholecystitis have been reported in GLP-1 receptor agonist trials and postmarketing. In placebo-controlled trials, cholelithiasis was reported in 1.5% and 0.4% of patients-treated with SEMBOLIC 0.5 mg and 1 mg, respectively. Cholelithiasis was not reported in placebo-treated patients. If cholelithiasis is suspected, gallbladder studies and appropriate clinical follow-up are indicated.
- Treatment with SEMBOLIC was associated with an increased occurrence of cholelithiasis and cholecystitis. The incidence of cholelithiasis and cholecystitis was higher in SEMBOLIC-treated pediatric patients aged 12 years and older than in SEMBOLIC-treated adults. In randomized clinical trials in adult patients, cholelithiasis was reported by 1.6% of SEMBOLIC-treated patients and 0.7% of placebo-treated patients. Cholecystitis was reported by 0.6% of SEMBOLIC-treated adult patients and 0.2% of placebo-treated patients. In a clinical trial in pediatric patients aged 12 years and older, cholelithiasis was reported by 3.8% of SEMBOLIC-treated patients and 0% placebo-treated patients. Cholecystitis was reported by 0.8% of SEMBOLIC-treated pediatric patients and 0% placebo-treated patients.
- Substantial or rapid weight loss can increase the risk of cholelithiasis; however, the incidence of acute gallbladder disease was greater in SEMBOLIC-treated patients than in placebo-treated patients, even after accounting for the degree of weight loss. If cholelithiasis is suspected, gallbladder studies and appropriate clinical follow-up are indicated.

**Heart Rate Increase**

- Treatment with SEMBOLIC was associated with increases in resting heart rate. Mean increases in resting heart rate of 1 to 4 beats per minute (bpm) were observed in SEMBOLIC-treated adult patients compared to placebo in clinical trials. More adult patients treated with SEMBOLIC compared with placebo had maximum changes from baseline at any visit of 10 to 19 bpm (41% versus 34%, respectively) and 20 bpm or more (26% versus 16%, respectively).
- In a clinical trial in pediatric patients aged 12 years and older with normal baseline heart rate, more patients treated with SEMBOLIC compared to placebo had maximum changes in heart rate of 20 bpm or more (54% versus 39%). Monitor heart rate at regular intervals consistent with usual clinical practice. Instruct patients to inform their healthcare providers of palpitations or feelings of a racing heartbeat while at rest during SEMBOLIC treatment. If patients experience a sustained increase in resting heart rate, discontinue SEMBOLIC.

**Suicidal Behaviour and Ideation**

- Suicidal behavior and ideation have been reported in clinical trials with other weight management products. Monitor patients treated with SEMBOLIC for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. Discontinue SEMBOLIC in patients who experience suicidal thoughts or behaviors. Avoid SEMBOLIC in patients with a history of suicidal attempts or active suicidal ideation.

**4.5 Drugs interactions**

**Concomitant Use with an Insulin Secretagogue (e.g., Sulfonylurea) or with Insulin**

- Semaglutide stimulates insulin release in the presence of elevated blood glucose concentrations. Patients receiving Semaglutide in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin may have an increased risk of hypoglycemia, including severe hypoglycemia. When initiating Semaglutide, consider reducing the dose of concomitantly administered insulin secretagogue (such as sulfonylureas) or insulin to reduce the risk of hypoglycemia.

**Oral Medications**

- Semaglutide causes a delay of gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications. In clinical pharmacology trials, semaglutide did not affect the absorption of orally administered medications to any clinically relevant degree. Nonetheless, caution should be exercised when oral medications are concomitantly administered Semaglutide

**4.6 Use in special populations**

**Pregnancy: Risk Summary**

There are limited data with semaglutide use in pregnant women to inform a drug-associated risk for adverse developmental outcomes. There are clinical considerations regarding the risks of poorly controlled diabetes in pregnancy. Based on animal reproduction studies, there may be potential risks to the fetus from exposure to semaglutide during pregnancy. SEMBOLIC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
In pregnant rats administered semaglutide during organogenesis, embryofetal mortality, structural abnormalities and alterations to growth occurred at maternal clinical exposure based on AUC. In rabbits and cynomolgus monkeys administered semaglutide during organogenesis, early pregnancy losses or structural abnormalities were observed at clinical exposure (rabbit) and ≥2-fold the MRHD (monkey). These findings coincided with a marked maternal body weight loss in both animal species (see Data).
In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively. The estimated background risk of major birth defects is 6 to 10% in women with pre-gestational diabetes with a peri-conceptional HbA1c >7 and has been reported to be as high as 20 to 25% in women with a peri-conceptional HbA1c >10. The estimated background risk of miscarriage for the indicated population is unknown.
*Clinical Considerations*
Disease-Associated Maternal and/or Embryo/fetal Risk
Hypoglycemia and hyperglycemia occur more frequently during pregnancy in patients with pre-gestational diabetes. Poorly controlled diabetes during pregnancy increases the maternal risk for diabetic ketoacidosis, pre- eclampsia, spontaneous abortions, preterm delivery, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.
Animal Data
In a combined fertility and embryofetal development study in rats, subcutaneous doses of 0.01, 0.03 and 0.09 mg/kg/day (0.06-, 0.2-, and 0.6-fold the MRHD) were administered to males for 4 weeks prior to and throughout mating and to females for 2 weeks prior to mating, and throughout organogenesis to Gestation Day 17. In parental animals, pharmacologically mediated reductions in body weight gain and food consumption were observed at all dose levels. In the offspring, reduced growth and fetuses with visceral (heart blood vessels) and skeletal (cranial bones, vertebra, ribs) abnormalities were observed at the human exposure.
In an embryofetal development study in pregnant rabbits, subcutaneous doses of 0.0010, 0.0025 or 0.0075 mg/kg/day (0.02-, 0.2-, and 1.2-fold the MRHD) were administered throughout organogenesis from Gestation Day 6 to 19. Pharmacologically mediated reductions in maternal body weight gain and food consumption were observed at all dose levels. Early pregnancy losses and increased incidences of minor visceral (kidney, liver) and skeletal (sternebra) fetal abnormalities were observed at ≥0.0025 mg/kg/day, at clinically relevant exposures.
In an embryofetal development study in pregnant cynomolgus monkeys, subcutaneous doses of 0.015, 0.075, and 0.15 mg/kg twice weekly (0.5-, 3-, and 8-fold the MRHD) were administered throughout organogenesis, from Gestation Day 16 to 50. Pharmacologically mediated, marked initial maternal body weight loss and reductions in body weight gain and food consumption coincided with the occurrence of sporadic abnormalities (vertebra, sternebra, ribs) at ≥0.075 mg/kg twice weekly (≥3X human exposure).
In a pre- and postnatal development study in pregnant cynomolgus monkeys, subcutaneous doses of 0.015, 0.075, and 0.15 mg/kg twice weekly (0.3-, 2-, and 4-fold the MRHD) were administered from Gestation Day 16 to 140. Pharmacologically mediated marked initial maternal body weight loss and reductions in body weight gain and food consumption coincided with an increase in early pregnancy losses and led to delivery of slightly smaller offspring at ≥0.075 mg/kg twice weekly (≥2X human exposure).

**Lactation - Risk Summary**

There are no data on the presence of semaglutide in human milk, the effects on the breastfed infant, or the effects on milk production. Semaglutide was present in the milk of lactating rats, however, due to species-specific differences in lactation physiology, the clinical relevance of these data are not clear (see Data). The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SEMBOLIC and any potential adverse effects on the breastfed infant from SEMBOLIC or from the underlying maternal condition.
Data
In lactating rats, semaglutide was detected in milk at levels 3-12 fold lower than in maternal plasma

**Females and Males of Reproductive Potential**

Discontinue SEMBOLIC in women at least 2 months before a planned pregnancy due to the long washout period for semaglutide.

**Pediatric Use**

Safety and efficacy of SEMBOLIC in T2DM have not been established in pediatric patients (younger than 18 years).
The safety and effectiveness of SEMBOLIC in chronic weight management have not been established in patients less than 12 years of age.

**Geriatric Use**

In the pool of placebo- and active-controlled glycemic control trials, 744 (23.6%) SEMBOLIC-treated patients were 65 years of age and over and 102 SEMBOLIC-treated patients (3.2%) patients were 75 years of age and over. In SUSTAIN 6, the cardiovascular outcome trial, 788 (48.0%) SEMBOLIC- treated patients were 65 years of age and over and 157 SEMBOLIC-treated patients (9.6%) patients were 75 years of age and over. No overall differences in safety or efficacy were detected between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.
In the SEMBOLIC clinical trials in chronic weight management, 233 (9%) SEMBOLIC-treated patients were between 65 and 75 years of age and 23 (1%) SEMBOLIC-treated patients were 75 years of age and over. No overall differences in safety or effectiveness have been observed between patients 65 years of age and older and younger adult patients.

**Renal Impairment**

No dose adjustment of SEMBOLIC is recommended for patients with renal impairment. In subjects with renal impairment including end-stage renal disease (ESRD), no clinically relevant change in semaglutide pharmacokinetics (PK) was observed.

**Hepatic Impairment**

No dose adjustment of SEMBOLIC is recommended for patients with hepatic impairment. In a study in subjects with different degrees of hepatic impairment, no clinically relevant change in semaglutide pharmacokinetics (PK) was observed.

**4.7 Effects on ability to drive and use machines**

Semaglutide has no or negligible influence on the ability to drive or use machines. When it is used in combination with a sulfonylurea or insulin, patients should be advised to take precautions to avoid hypoglycaemia while driving and using machines.

**4.8 Undesirable effects**

**T2DM:**

The most frequently reported adverse reaction(s) with Semaglutide are nausea, vomiting, diarrhea, abdominal pain and constipation. Other common reaction(s) includes reduction in blood sugar, dizziness, eye complications, difficulty in digestion, heart-burn, gall-bladder stone, generalized weakness, increase pancreatic enzymes etc. Uncommon reaction(s) includes injection site reaction, increased heart rate, acute pancreatitis, allergic reaction etc. Rare reaction(s) includes severe allergic reactions and intestinal obstruction.

**Table 3** shows common adverse reactions, excluding hypoglycemia, associated with the use of SEMBOLIC in the pool of placebo-controlled trials. These adverse reactions occurred more commonly on SEMBOLIC than on placebo and occurred in at least 5% of patients treated with SEMBOLIC.

| Adverse reaction | Placebo (N=262) % | SEMBOLIC 0.5 mg (N=260) % | SEMBOLIC 1 mg (N=261) % |
|---|---|---|---|
| Nausea | 6.1 | 15.8 | 20.3 |
| Vomiting | 2.3 | 5.0 | 9.2 |
| Diarrhea | 1.9 | 8.5 | 8.8 |
| Abdominal pain | 4.6 | 7.3 | 5.7 |
| Constipation | 1.5 | 5.0 | 3.1 |

**Table 4** shows summarizes the incidence of events related to hypoglycemia by various definitions in the placebo-controlled trials.

| | Placebo | SEMBOLIC 0.5 Mg | SEMBOLIC 1 mg |
|---|---|---|---|
| **Monotherapy** | | | |
| (30 weeks) | N=129 | N=127 | N=130 |
| Severe† | 0% | 0% | 0% |
| Documented symptomatic (≤70 mg/dL glucose threshold) | 0% | 1.6% | 3.8% |
| Severe† or Blood Glucose Confirmed Symptomatic (≤56 mg/dL glucose threshold) | 1.6% | 0% | 0% |
| **Add-on to Basal Insulin with or without Metformin** | | | |
| (30 weeks) | N=132 | N=132 | N=131 |
| Severe† | 0% | 0% | 1.5% |
| Documented symptomatic (≤70 mg/dL glucose threshold) | 15.2% | 16.7% | 29.8% |
| Severe† or Blood Glucose Confirmed Symptomatic (≤56 mg/dL glucose threshold) | 5.3% | 8.3% | 10.7% |

† "Severe" hypoglycemia adverse reactions are episodes requiring the assistance of another person.

**Injection Site Reactions**

In placebo-controlled trials, injection site reactions (e.g., injection-site discomfort, erythema) were reported in 0.2% of SEMBOLIC-treated patients.

**Increases in Amylase and Lipase**

In placebo-controlled trials, patients exposed to SEMBOLIC had a mean increase from baseline in amylase of 13% and lipase of 22%. These changes were not observed in placebo-treated patients.

**Cholelithiasis**

In placebo-controlled trials, cholelithiasis was reported in 1.5% and 0.4% of patients-treated with SEMBOLIC 0.5 mg and 1 mg, respectively. Cholelithiasis was not reported in placebo-treated patients.

**Increases in Heart Rate**

In placebo-controlled trials, SEMBOLIC 0.5 mg and 1 mg resulted in a mean increase in heart rate of 2 to 3 beats per minute. There was a mean decrease in heart rate of 0.3 beats per minute in placebo-treated patients.

**Fatigue, Dysgeusia and Dizziness**

Other adverse reactions with a frequency of >0.4% were associated with SEMBOLIC include fatigue, dysgeusia and dizziness.

**CHRONIC WEIGHT MANAGEMENT:**

**Adverse Reactions in Clinical Trials in Adults with Obesity or Overweight**

SEMBOLIC 2.4 mg Subcutaneous Weekly Dosage
SEMBOLIC was evaluated for safety in 3 randomized, double-blind, placebo-controlled trials that included 2,116 adult patients with overweight or obesity treated with 2.4 mg SEMBOLIC for up to 68 weeks and a 7 week off drug follow-up period.
Baseline characteristics included a mean age of 48 years, 71% women, 72% White, 14% Asian, 9% Black or African American, and 5% reported as other or unknown; and 85% were not Hispanic or Latino ethnicity, 13% were Hispanic or Latino ethnicity and 2% reported as unknown. The baseline characteristics were 42% with hypertension, 19% with type 2 diabetes, 43% with dyslipidemia, 28% with a BMI greater than 40 kg/m$^2$, and 4% with cardiovascular disease.
In clinical trials, 6.8% of patients treated with 2.4 mg SEMBOLIC and 3.2% of patients treated with placebo permanently discontinued treatment as a result of adverse reactions. The most common adverse reactions leading to discontinuation were nausea (1.8% versus 0.2%), vomiting (1.2% versus 0%), and diarrhea (0.7% versus 0.1%) for SEMBOLIC and placebo, respectively.
**Table 5 -** Adverse Reactions (> 2% and Greater Than Placebo) in SEMBOLIC-treated Adult with Obesity or Overweight for Chronic Weight Management

| | Placebo N=1,261 % | SEMBOLIC 2.4 mg N=2,116 % |
|---|---|---|
| Nausea | 16 | 44 |
| Diarrhea | 16 | 30 |
| Vomiting | 6 | 24 |
| Constipation | 11 | 24 |
| Abdominal Pain[a] | 10 | 20 |
| Headache | 10 | 14 |
| Fatigue[b] | 5 | 11 |
| Dyspepsia | 3 | 9 |
| Dizziness | 4 | 8 |
| Abdominal Distension | 5 | 7 |
| Eructation | <1 | 7 |
| Hypoglycemia in T2DM[c] | 2 | 6 |
| Flatulence | 4 | 6 |
| Gastroenteritis | 4 | 6 |
| Gastroesophageal Reflux Disease | 3 | 5 |
| Gastritis[d] | 1 | 4 |
| Gastroenteritis Viral | 3 | 4 |
| Hair Loss | 1 | 3 |
| Dysesthesiae | 1 | 2 |

[a] Includes abdominal pain, abdominal pain upper, abdominal pain lower, gastrointestinal pain, abdominal tenderness, abdominal discomfort and epigastric discomfort [b] Includes fatigue and asthenia [c] Defined as blood glucose <54 mg/dL with or without symptoms of hypoglycemia or severe hypoglycemia (requiring the assistance of another person) in patients with type 2 diabetes not on concomitant insulin (Study 3, SEMBOLIC N=403, Placebo N=402). See text below for further information regarding hypoglycemia in patients with and without type 2 diabetes. T2DM = type 2 diabetes mellitus [d] Includes chronic gastritis, gastritis, gastritis erosive, and reflux gastritis [e] Includes paresthesia, hyperesthesia, burning sensation, allodynia, dysesthesia, skin burning sensation, pain of skin, and sensitive skin

SEMBOLIC 1.7 mg Subcutaneous Weekly Dosage
SEMBOLIC 1.7 mg subcutaneous weekly was evaluated for safety in a 68-week, randomized, double-blind, parallel-group, placebo-controlled trial in 401 patients with overweight or obesity. Adverse reactions observed with SEMBOLIC 1.7 mg were similar to those reported with SEMBOLIC 2.4 mg.

**Other Adverse Reactions**

Acute Pancreatitis
In SEMBOLIC clinical trials in adults, acute pancreatitis was confirmed by adjudication in 4 SEMBOLIC-treated patients (0.2 cases per 100 patient years) versus 1 in placebo-treated patients (less than 0.1 cases per 100 patient years). One additional case of acute pancreatitis was confirmed in a patient treated with SEMBOLIC in another clinical trial.
Acute Gallbladder Disease
In SEMBOLIC clinical trials in adults, cholelithiasis was reported by 1.6% of SEMBOLIC-treated patients and 0.7% of placebo-treated patients. Cholecystitis was reported by 0.6% of SEMBOLIC-treated adult patients and 0.2% of placebo-treated patients. In a clinical trial in pediatric patients aged 12 years and older, cholelithiasis was reported by 3.8% of SEMBOLIC-treated patients and 0% placebo-treated patients. Cholecystitis was reported by 0.8% of SEMBOLIC-treated pediatric patients and 0% placebo-treated patients.
Hypoglycemia
Patients with Type 2 Diabetes
In a trial of adult patients with type 2 diabetes and BMI greater than or equal to 27 kg/m$^2$, clinically significant hypoglycemia (defined as a plasma glucose less than 54 mg/dL) was reported in 6.2% of SEMBOLIC-treated patients versus 2.5% of placebo-treated patients. A higher rate of clinically significant hypoglycemic episodes was reported with SEMBOLIC (semaglutide 2.4 mg) versus semaglutide 1 mg (10.7 vs. 7.2 episodes per 100 patient years of exposure, respectively); the rate in the placebo-treated group was 3.2 episodes per 100 patient years of exposure. In addition, one episode of severe hypoglycemia requiring intravenous glucose was reported in a SEMBOLIC-treated patient versus none in placebo-treated patients. The risk of hypoglycemia was increased when SEMBOLIC was used with a sulfonylurea.
Patients without Type 2 Diabetes
Episodes of hypoglycemia have been reported with GLP-1 receptor agonists in adult patients without type 2 diabetes mellitus. In SEMBOLIC clinical trials in adult patients without type 2 diabetes mellitus, there was no systematic capturing or reporting of hypoglycemia.
Acute Kidney Injury
Acute kidney injury occurred in clinical trials in 7 adult patients (0.4 cases per 100 patient years) receiving SEMBOLIC versus 4 patients (0.2 cases per 100 patient years of exposure) receiving placebo. Some of these adverse reactions occurred in association with gastrointestinal adverse reactions or dehydration. In addition, 2 patients treated with SEMBOLIC had acute kidney injury with dehydration in other clinical trials. The risk of renal adverse reactions with SEMBOLIC was increased in adult patients with a history of renal impairment (trials included 65 patients with a history of moderate or severe renal impairment at baseline), and occurred more frequently during dose titration.
Retinal Disorders in Patients with Type 2 Diabetes
In a trial of adult patients with type 2 diabetes and BMI greater than or equal to 27 kg/m$^2$, retinal disorders were reported by 6.9% of patients treated with SEMBOLIC (semaglutide 2.4 mg), 6.2% of patients treated with semaglutide 1 mg, and 4.2% of patients treated with placebo. The majority of events were reported as diabetic retinopathy (4.0%, 2.7%, and 2.7%, respectively) and non-proliferative retinopathy (0.7%, 0%, and 0%, respectively).
Increase in Heart Rate
Mean increases in resting heart rate of 1 to 4 beats per minute (bpm) were observed with routine clinical monitoring in SEMBOLIC-treated adult patients compared to placebo in clinical trials.
In trials in which adult patients were randomized prior to dose-escalation, more patients treated with SEMBOLIC, compared with placebo, had maximum changes from baseline at any visit of 10 to 19 bpm (41% versus 34%, respectively) and 20 bpm or more (26% versus 16%, respectively). In a clinical trial in pediatric patients aged 12 years and older with normal baseline heart rate, more patients treated with SEMBOLIC compared to placebo had maximum changes in heart rate of 20 bpm or more (54% versus 39%).
Hypotension and Syncope
Adverse reactions related to hypotension (hypotension, orthostatic hypotension, and decreased blood pressure) were reported in 1.3% of SEMBOLIC-treated adult patients versus 0.4% of placebo-treated patients and syncope was reported in 0.8% of SEMBOLIC-treated patients versus 0.2% of placebo-treated patients. Some reactions were related to gastrointestinal adverse reactions and volume loss associated with SEMBOLIC. Hypotension and orthostatic hypotension were more frequently seen in patients on concomitant antihypertensive therapy. In a clinical trial in pediatric patients aged 12 years and older, hypotension was reported in 2.3% of SEMBOLIC treated patients versus 0% in placebo-treated patients.
Appendicitis
Appendicitis (including perforated appendicitis) occurred in 10 (0.5%) SEMBOLIC-treated adult patients and 2 (0.2%) patients receiving placebo.
Gastrointestinal Adverse Reactions
In clinical trials in adults, 73% of SEMBOLIC-treated patients and 47% of patients receiving placebo reported gastrointestinal disorders. The most frequently reported reactions were nausea (44% vs. 16%), vomiting (25% vs. 6%), and diarrhea (30% vs. 16%). Other common reactions that occurred at a higher incidence among SEMBOLIC-treated adult patients included dyspepsia, abdominal pain, abdominal distension, eructation, flatulence, gastroesophageal reflux disease, gastritis, and hemorrhoids. These reactions increased during dose escalation.
In a pediatric clinical trial, 62% of SEMBOLIC-treated patients and 42% of placebo-treated patients reported gastrointestinal disorders. The most frequently reported reactions were nausea (42% vs. 18%), vomiting (36% vs. 10%), and diarrhea (22% vs. 19%). Other gastrointestinal-related reactions that occurred at a higher incidence than placebo among SEMBOLIC-treated pediatric patients included abdominal pain, constipation, eructation, gastroesophageal reflux disease, dyspepsia, and flatulence. Permanent discontinuation of treatment as a result of a gastrointestinal adverse reaction occurred in 4.3% of SEMBOLIC-treated adult patients versus 0.7% of placebo-treated patients. In a pediatric clinical trial, 2.3% of patients treated with SEMBOLIC versus 1.5% of patients who received placebo discontinued treatment as a result of gastrointestinal adverse reactions.
Injection Site Reactions
In clinical trials in adults, 1.4% of SEMBOLIC-treated patients and 1.0% of patients receiving placebo experienced injection site reactions (including injection site pruritus, erythema, inflammation, induration, and irritation).
Hypersensitivity Reactions
Serious hypersensitivity reactions (e.g., anaphylaxis, angioedema) have been reported with SEMBOLIC. In a pediatric clinical trial, rash was reported in 3% of SEMBOLIC-treated patients and 0% of placebo-treated patients, and urticaria was reported in 3% of SEMBOLIC-treated patients and 0% of placebo-treated patients. In adult clinical trials, allergic reactions occurred in 8/50 (16%) of SEMBOLIC-treated patients with anti-semaglutide antibodies and in 114/1659 (7%) of SEMBOLIC-treated patients who did not develop antisemaglutide antibodies.
Dysgeusia
In clinical trials in adults, 1.7% of SEMBOLIC-treated patients and 0.5% of placebo-treated patients reported dysgeusia.
Laboratory Abnormalities
Amylase and Lipase
Adult and pediatric patients treated with SEMBOLIC had a mean increase from baseline in amylase of 15-16% and lipase of 39%. These changes were not observed in the placebo group. The clinical significance of elevations in lipase or amylase with SEMBOLIC is unknown in the absence of other signs and symptoms of pancreatitis.
Liver Enzymes
In a pediatric clinical trial, increases in alanine aminotransferase (ALT) greater than or equal to 5 times the upper limit of normal were observed in 4 (3%) SEMBOLIC-treated patients compared with 0% of placebo treated patients. In some patients, increases in ALT and AST were associated with other confounding factors (such as gallstones).

**4.9 Overdose**

Overdoses have been reported with other GLP-1 receptor agonists. Effects have included severe nausea, severe vomiting, and severe hypoglycemia. In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.
A prolonged period of observation and treatment for these symptoms may be necessary, taking into account the long half-life of SEMBOLIC of approximately 1 week.

**5. Pharmacological properties**

**5.1 Mechanism of Action**

SEMBOLIC is a GLP-1 analogue with 94% sequence homology to human GLP-1. Semaglutide acts as a GLP-1 receptor agonist that selectively binds to and activates the GLP-1 receptor, the target for native GLP-1. GLP-1 is a physiological hormone that has multiple actions on glucose, mediated by the GLP-1 receptors. The principal mechanism of protraction resulting in the long half-life of semaglutide is albumin binding, which results in decreased renal clearance and protection from metabolic degradation. Furthermore, semaglutide is stabilized against degradation by the DPP-4 enzyme.
Semaglutide reduces blood glucose through a mechanism where it stimulates insulin secretion and lowers glucagon secretion, both in a glucose-dependent manner. Thus, when blood glucose is high, insulin secretion is stimulated, and glucagon secretion is inhibited. The mechanism of blood glucose lowering also involves a minor delay in gastric emptying in the early postprandial phase.
GLP-1 is a physiological regulator of appetite and caloric intake, and the GLP-1 receptor is present in several areas of the brain involved in appetite regulation. Animal studies show that semaglutide distributed to and activated neurons in brain regions involved in regulation of food intake.

**5.2 Pharmacodynamic properties**

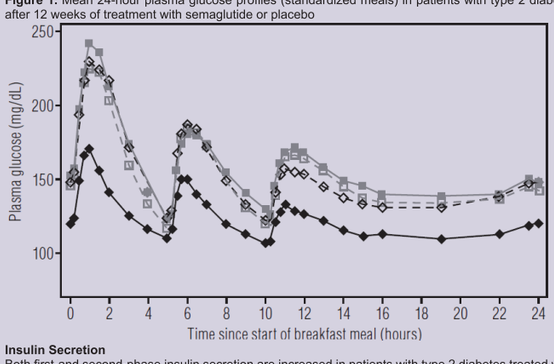
**T2DM:**

Semaglutide lowers fasting and postprandial blood glucose and reduces body weight. All pharmacodynamic evaluations were performed after 12 weeks of treatment (including dose escalation) at steady state with semaglutide 1 mg.

**Fasting and Postprandial Glucose**

Semaglutide reduces fasting and postprandial glucose concentrations. In patients with type 2 diabetes, treatment with semaglutide 1 mg resulted in reductions in glucose in terms of absolute change from baseline and relative reduction compared to placebo of 29 mg/dL (22%) for fasting glucose, 74 mg/dL (36%) for 2-hour postprandial glucose, and 30 mg/dL (22%) for mean 24-hour glucose concentration (see Figure 1).

**Figure 1.** Mean 24-hour plasma glucose profiles (standardized meals) in patients with type 2 diabetes before (baseline) and after 12 weeks of treatment with semaglutide or placebo




**Insulin Secretion**

Both first-and second-phase insulin secretion are increased in patients with type 2 diabetes treated with SEMBOLIC compared with placebo.

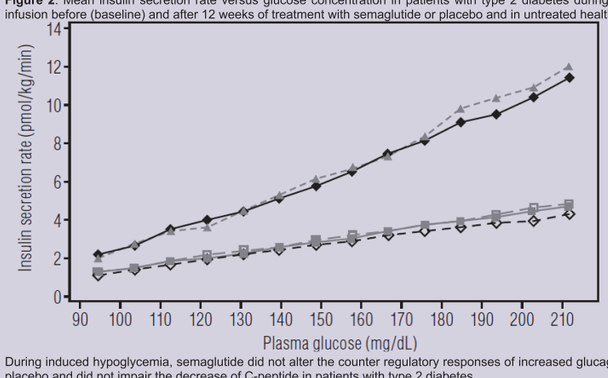
**Glucagon Secretion**

Semaglutide lowers the fasting and postprandial glucagon concentrations. In patients with type 2 diabetes, treatment with semaglutide resulted in the following relative reductions in glucagon compared to placebo, fasting glucagon (8%), postprandial glucagon response (14-15%), and mean 24 hour glucagon concentration (12%).

**Glucose dependent insulin and glucagon secretion**

Semaglutide lowers high blood glucose concentrations by stimulating insulin secretion and lowering glucagon secretion in a glucose-dependent manner. With semaglutide, the insulin secretion rate in patients with type 2 diabetes was similar to that of healthy subjects.

**Figure 2**. Mean insulin secretion rate versus glucose concentration in patients with type 2 diabetes during graded glucose infusion before (baseline) and after 12 weeks of treatment with semaglutide or placebo and in untreated healthy subjects.




During induced hypoglycemia, semaglutide did not alter the counter regulatory responses of increased glucagon compared to placebo and did not impair the decrease of C-peptide in patients with type 2 diabetes.

**Gastric emptying**

Semaglutide causes a delay of early postprandial gastric emptying, thereby reducing the rate at which glucose appears in the circulation postprandially.

**Cardiac electrophysiology (QTc)**

The effect of semaglutide on cardiac repolarization was tested in a thorough QTc trial. Semaglutide does not prolong QTc intervals at doses up to 1.5 mg at steady-state.

- Clinical efficacy and safety - Summary from Phase III clinical trial in T2DM conducted by Zydus Lifesciences Limited

A Phase III, Multicenter, Randomized, Comparative, Active-Controlled, Open Label Study was conducted to Evaluate the Efficacy and Safety of Semaglutide Injection in Comparison with Reference Biologic in Type 2 Diabetes Mellitus. Test product was Semaglutide Injection 15 mg/3 mL (5 mg/mL) manufactured by M/s. Zydus Lifesciences Limited and Comparator Product was Reference Biologic Injection (Semaglutide) 2 mg/1.5 mL (1.34 mg/mL) pre-filled pen, 4 mg/3 mL (1.34 mg/mL) pre-filled pen and 8 mg/3 mL (2.68 mg/mL) pre-filled pen manufactured by M/s. Novo Nordisk.
This study was conducted in male and female patients aged 18 to 65 years (both inclusive), diagnosed with type 2 diabetes mellitus having glycosylated haemoglobin (HbA1c) ≥ 7.0% and ≤ 10.5%, who were on diet and exercise control and receiving a stable daily dose of Metformin (≥ 1500 mg or the maximum tolerated dose, as documented in clinical records) for at least 12 weeks prior to the screening visit.
The enrolled patients were assigned to either of the two study groups according to a centralized computer-generated randomization in a 1:1 ratio. A total of 346 patients were screened, 314 patients were randomized and 274 patients completed the study for 24 weeks. This study was conducted in total 24 clinical trial sites in India and all the sites had obtained approval from the respective Institutional/Independent Ethics Committees prior to the study initiation.
The primary efficacy endpoint was the change in HbA1c from baseline at the end of Week 24. In the PP population (N = 294), the LSM ± SE reduction in HbA1c from baseline to Week 24 was −1.75 ± 0.07% for the Test Product and −1.70 ± 0.07% for the Comparator Product, with an LS-mean difference of −0.054% (95% CI: −0.24 to 0.13; p = 0.5726). These results were consistent with those of the mITT analysis, confirming the robustness of non-inferiority.

**Table 6: Change in HbA1c from baseline at the end of Week 24.**

| Visit | Statistics | Test Product (N=143) | Comparator Product (N=151) |
|---|---|---|---|
| Baseline | Mean (SD) | 8.33 (0.84) | 8.34 (0.86) |
| | Median | 8.20 | 8.20 |
| | (Min, Max) | (7.00, 10.50) | (7.00, 10.50) |
| Week 24 | Mean (SD) | 6.61 (0.60) | 6.66 (0.62) |
| | Median | 6.60 | 6.70 |
| | (Min, Max) | (5.40, 8.40) | (5.20, 8.60) |
| Change from baseline to Week 24 | LSM (SE) | -1.7545 (0.0688) | -1.7005 (0.0664) |
| | LS mean difference | -0.0540 | |
| | 95% CI of LS mean difference | (-0.24, 0.13) | |
| | *P*-value | 0.5726 | |

Secondary efficacy endpoints including change from baseline in Fasting Plasma Glucose (FPG), 2-hour Post-Prandial Glucose (PPG), body weight, BMI, SBP, DBP and fasting lipid profile were evaluated using both the mITT and PP populations. Across all secondary efficacy parameters, no statistically significant differences were observed between the Test Product and Comparator Product arms at any evaluated time point. Both treatment arms demonstrated a comparable magnitude of improvement from baseline, indicating that glycaemic control and associated metabolic effects were similar between treatments.
The proportion of participants achieving HbA1c < 7.0 % at Weeks 8, 12, 16, 20, and 24 increased progressively across both treatment arms. The results were comparable between the two groups in both analysis populations, further substantiating the conclusion of non-inferiority for glycaemic efficacy.
Both the mITT and PP analyses confirmed that the Test Product was non-inferior to the Comparator Product with respect to the primary efficacy endpoint (change in HbA1c) and demonstrated no significant differences in any of the secondary efficacy endpoints.
In terms of safety evaluation, total 534 adverse events were reported in 189 patients. 265 adverse events were reported in test product and 269 adverse events were reported in comparator product. 14 adverse events from test product and 17 adverse events from comparator product were moderate in nature; all the other adverse events were mild in nature. No serious adverse events were reported during the study. No clinically significant changes were observed in clinical laboratory parameters, vital signs (pulse rate, respiratory rate, body temperature, systolic and diastolic blood pressure), systemic examination findings, 12-lead ECG results, or routine urinalysis in either of the treatment groups.
These results collectively establish that the Test Product provides equivalent glycaemic efficacy and clinical benefit to the Comparator Product throughout the 24-week treatment period.

**CHRONIC WEIGHT MANAGEMENT:**

Semaglutide lowers body weight through decreased calorie intake. The effects are likely mediated by affecting appetite. Semaglutide stimulates insulin secretion and reduces glucagon secretion in a glucose-dependent manner. These effects can lead to a reduction of blood glucose.
Cardiac electrophysiology (QTc)

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|---|---|---|---|---|---|---|---|
| **PRODUCT NAME :** | SEMBOLIC Inj. | **COUNTRY :** Domestic P2P | **LOCATION :** Zydus Life. | | **SUPERSEDES A/W NO. :** | | |
| **ITEM / PACK :** | Insert_ | **NO. OF COLORS : 4** | **SUBSTRATE :** | | | | |
| **DESIGN STYLE :** | Back | **PANTONE SHADE Nos. :** | **REMARK :** | | | | |
| **CODE :** | XXXXXXX -9093 | **CMYK** | **Activities** | **Department** | **Name** | **Signature** | **Date** |
| **DIMENSION (MM) :** | S/S | | **Prepared By** | **Pkg.Dev** | | | |
| **ART WORK SIZE :** | 230 x 560 mm | | **Reviewed By** | **Pkg.Dev** | | | |
| **DATE :** | 12-02-2026 | | **Reviewed By** | **CR** | | | |
| | | | **Approved By** | **Quality** | | | |
| | | | **Approved By** | **Quality** | | | |

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