

Trulicity™ (dulaglutide) Medical Value Summary

- TRULICITY is a glucagon-like peptide (GLP-1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM).¹
- Developed for once-weekly administration, TRULICITY is a glucagon-like peptide (GLP-1) receptor agonist studied as monotherapy, add on to metformin, add on to metformin and pioglitazone, add on to metformin and sulfonylureas, and add on to prandial insulin to improve glycemic control in adult patients with T2DM.²
- Dulaglutide exhibits GLP-1-mediated effects, including glucose-dependent potentiation of insulin secretion, inhibition of glucagon secretion, slowing of gastric emptying, and increased satiety.⁴
- The combination of these effects results in a decrease of both fasting and postprandial glucose (PPG) concentrations which can be observed after a single dose, thereby leading to improvement in overall glycemic control.⁴
- Further enhancement in long-term glycemic control may be achieved by improvements in weight control and pancreatic β -cell function.^{3,5,8,10,12}
- Dulaglutide is the only weekly GLP-1 receptor agonist that has demonstrated noninferiority to liraglutide in HbA1c change from baseline.^{3, 13,14}

Efficacy Summary

- TRULICITY has been studied as monotherapy and in combination with metformin, metformin and thiazolidinedione, metformin and sulfonylurea, and prandial insulin with or without metformin.²

Trial Acronym	Concomitant therapy	Active comparator	Efficacy (% HbA _{1c}) at primary endpoint		
			Dulaglutide 1.5mg	Dulaglutide 0.75mg	Comparator
AWARD-1 ⁸	Metformin and Thiazolidinedione	Exenatide twice daily	-1.51 ± 0.06	-1.30 ± 0.06	-0.99 ± 0.06
AWARD-2 ⁹	Metformin and Sulfonylurea	Insulin glargine	-1.08 ± 0.06	-0.76 ± 0.06	-0.63 ± 0.06
AWARD-3 ¹⁰	Monotherapy	Metformin	-0.78 ± 0.06	-0.71 ± 0.06	-0.56 ± 0.06
AWARD-4 ¹¹	Insulin lispro with/without metformin	Insulin glargine	-1.64 ± 0.07	-1.59 ± 0.07	-1.41 ± 0.07
AWARD-5 ¹²	Metformin	Sitagliptin	-1.10 ± 0.06	-0.87 ± 0.06	-0.39 ± 0.06
AWARD-6 ¹³	Metformin	Liraglutide	-1.42 ± 0.06	Not studied	-1.36 ± 0.06

- The studies evaluated the use of TRULICITY 0.75 mg and 1.5 mg (except AWARD-6 which studied 1.5 mg only). Patients were initiated and maintained on either 0.75 mg or 1.5 mg for the duration of the trials.²
- No overall differences in glycemic effectiveness were observed across demographic subgroups (age, gender, race/ethnicity, duration of diabetes).²

Safety Summary

Please see full prescribing information for complete safety information.

The FDA has required this safety notice as part of the TRULICITY REMS (Risk Evaluation and Mitigation Strategy) to inform healthcare providers about the following **serious risks of TRULICITY (dulaglutide)**:

- **Potential Risk of Medullary Thyroid Carcinoma (MTC).** Thyroid C-cell tumors have been observed in rodent studies with glucagon-like peptide (GLP-1) receptor agonists. It is unknown whether TRULICITY causes thyroid C-cell tumors, including MTC, in humans. Counsel patients regarding the risk of MTC and the symptoms of thyroid tumors.
- TRULICITY has a **boxed warning** on the risk of thyroid c-cell tumors. Dulaglutide causes thyroid C-cell tumors in rats. It is unknown whether TRULICITY causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as human relevance could not be determined from clinical or nonclinical studies. TRULICITY is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2)⁶.
- **Risk of Pancreatitis.** Pancreatitis has been reported with the use of GLP-1 receptor agonists. Cases of pancreatitis have been described in association with TRULICITY during clinical trials. Discontinue

promptly if pancreatitis is suspected. Do not restart if pancreatitis is confirmed. Consider other antidiabetic therapies in patients with a history of pancreatitis.

TRULICITY is not recommended as first-line therapy for patients with type 2 diabetes mellitus inadequately controlled on diet and exercise. Please visit www.TRULICITYREMS.com for more information.

- The most common adverse reactions, reported in $\geq 5\%$ of patients treated with TRULICITY are: nausea, diarrhea, vomiting, abdominal pain, and decreased appetite.⁷

TRULICITY Value Summary

- TRULICITY has demonstrated efficacy improving glycemic control in adult patients with T2DM .
- TRULICITY results in a decrease of both fasting and postprandial glucose (PPG) concentrations which can be observed after a single dose, thereby leading to improvement in overall glycemic control.⁴
- No overall differences in glycemic effectiveness were observed across demographic subgroups (age, gender, race/ethnicity, duration of diabetes).
- TRULICITY is available as a once weekly injection delivered via a single-dose pen device that has a hidden, attached, self retracting needle and requires no reconstitution.
- No dosage adjustment is indicated for patients with renal impairment.
- TRULICITY has a proven safety and tolerability profile similar to the class.
- The American Diabetes Association's Standards of Medical Care in Diabetes (2014) recommends the addition of GLP-1 receptor agonists to metformin for patients at the maximally tolerated dose and not achieving or maintaining HbA_{1c} targets over 3 months as one of the suggested two-drug combinations based on patient profiles and needs.¹⁵
- The American Association Of Clinical Endocrinologists (AACE) Comprehensive Diabetes Management Algorithm (2013) recommends the use of GLP-1 receptor agonists as monotherapy, dual therapy or triple therapy based on the entry HbA_{1c} of patients. GLP-1s are suggested second on the hierarchy to metformin.¹⁷
- TRULICITY is the only weekly GLP-1 receptor agonist to demonstrate noninferiority to once-daily liraglutide in HbA_{1c} change from baseline.^{3, 13, 14}

REFERENCES

1. TRULICITY (dulaglutide) Prescribing Information. Indianapolis, IN: Eli Lilly and Company, September 2014 [Section 1: Indications and Usage]
2. TRULICITY (dulaglutide) Prescribing Information. Indianapolis, IN: Eli Lilly and Company, September 2014 [Section 14: Clinical Studies]
3. Dungan KM, Povedano ST, Forst T, González JG, Atisso C, Sealls W, Fahrbach JL. Once-weekly dulaglutide versus once-daily liraglutide in metformin-treated patients with type 2 diabetes (AWARD-6): a randomized, open-label, phase 3, non-inferiority trial. *Lancet*. 2014;384:1349-1357.
4. TRULICITY (dulaglutide) Prescribing Information. Indianapolis, IN: Eli Lilly and Company, September 2014 [Section 12.1 and 12.2]
5. TRULICITY AMCP Dossier, Approved October 2014. [Section 1, Clinical Benefits]
6. TRULICITY (dulaglutide) Prescribing Information. Indianapolis, IN: Eli Lilly and Company, September 2014 [Sections 4.1, 5.1 and 13.1]
7. TRULICITY (dulaglutide) Prescribing Information. Indianapolis, IN: Eli Lilly and Company, September 2014 [Section 6.1]
8. Carol Wysham, Thomas Blevins, Richard Arakaki, Gildred Colon, Pedro Garcia, Charles Atisso, Debra Kuhstoss, and Mark Lakshmanan. Efficacy and Safety of Dulaglutide Added Onto Pioglitazone and Metformin Versus Exenatide in Type 2 Diabetes in a Randomized Controlled Trial (AWARD-1). *Diabetes Care* August 2014 37:2159-2167. doi:10.2337/dc13-2760
9. [AWARD 2] Abstract 330-OR, 74th American Diabetes Association (ADA) Scientific Sessions, 13-17 June 2014, San Francisco, CA, USA.
10. Guillermo Umpierrez, Santiago Tofé Povedano, Federico Pérez Manghi, Linda Shurzinske, and Valeria Pechter. Efficacy and Safety of Dulaglutide Monotherapy Versus Metformin in Type 2 Diabetes in a Randomized Controlled Trial (AWARD-3). *Diabetes Care* August 2014 37:2168-2176. doi:10.2337/dc13-2759
11. [AWARD 4] Abstract 979-P, 74th American Diabetes Association (ADA) Scientific Sessions, 13-17 June 2014, San Francisco, CA, USA
12. Michael Nauck, Ruth S. Weinstock, Guillermo E. Umpierrez, Bruno Guerci, Zachary Skrivanek, and Zvonko Milicevic. Efficacy and Safety of Dulaglutide Versus Sitagliptin After 52 Weeks in Type 2 Diabetes in a Randomized Controlled Trial (AWARD-5) *Diabetes Care* August 2014 37:2149-2158. doi:10.2337/dc13-2761
13. Once-weekly albiglutide versus once-daily liraglutide in patients with type 2 diabetes inadequately controlled on oral drugs (HARMONY 7): a randomised, open-label, multicentre, non-inferiority phase 3 study. Richard E Pratley, Michael A Nauck, Anthony H Barnett, Mark N Feinglos, Fernando Ovalle, Illana Harman-Boehm, June Ye, Rhona Scott, Susan Johnson, Murray Stewart, Julio Rosenstock. *The Lancet Diabetes & Endocrinology* 1 April 2014 (Volume 2 Issue 4 Pages 289-297 DOI: 10.1016/S2213-8587(13)70214-6)
14. John B Buse, Michael Nauck, Thomas Forst, Wayne H-H Sheu, Sylvia K Shenouda, Cory R Heilmann, Byron J Hoogwerf, Aijun Gao, Marilyn K Boardman, Mark Fineman, Lisa Porter, Guntram Schernthaner, Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study, *The Lancet*, Volume 381, Issue 9861, 12–18 January 2013, Pages 117-124, ISSN 0140-6736, doi:10.1016/S0140-6736(12)61267-7.
15. Position Statement: American Diabetes Association. Standards of Medical Care in Diabetes—2014 *Diabetes Care* January 2014 37:Supplement 1 S14-S80; doi:10.2337/dc14-S014
16. Garber, A., et al. (2013). "ACE Comprehensive Diabetes Management Algorithm." *Endocrine Practice* 19(12): 327-336.