Therapeutic Class Overview
Meglitinides

Therapeutic Class

- **Overview/Summary:** The meglitinides and the sulfonylureas are two classes of oral antidiabetic medications utilized in the management of type 2 diabetes mellitus that work by stimulating the release of insulin from pancreatic β-cells. While the meglitinide and sulfonylurea agents differ in chemical structure and act on different receptors, both medication classes act by regulating potassium channels in pancreatic β-cells, thereby increasing insulin secretion.[1] The available meglitinides, nateglinide (Starlix®) and repaglinide (Prandin®), are Food and Drug Administration (FDA)-approved as adjunct therapy to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Nateglinide and repaglinide are both available as single-entity agents, and repaglinide is also available as a fixed-dose combination product with metformin (PrandiMet®). Metformin, a biguanide, improves glucose tolerance in type 2 diabetics by lowering both basal and postprandial plasma glucose. Specifically, the actions of metformin result in decreased hepatic glucose production, decreased intestinal absorption of glucose, and improvement in insulin sensitivity via increased peripheral glucose uptake and utilization. The repaglinide/metformin combination product is FDA-approved for patients already treated with a meglitinide and metformin or for patients who have inadequate glycemic control on a meglitinide or metformin alone. Due to their mechanism of action and pharmacokinetic profiles, the meglitinides are dosed three times daily with meals.[2-4] Currently, nateglinide, repaglinide, and the repaglinide/metformin combination are all available generically.

Table 1. Current Medications Available in the Class[2-4]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Single-Entity Agents			
Nateglinide (Starlix®*)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	Tablet: 60 mg 120 mg	✔
Repaglinide (Prandin®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	Tablet: 0.5 mg 1 mg 2 mg	✔
Combination Products			
Repaglinide/ metformin (PrandiMet®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are already treated with a meglitinide and metformin or who have inadequate glycemic control on a meglitinide alone or metformin alone	Tablet: 1/500 mg 2/500 mg	✔

*Generic available in at least one dosage form or strength.

Evidence-based Medicine

- Available evidence suggests that the sulfonylureas may be associated with poorer outcomes following myocardial infarction in patients with diabetes.[1] Specifically, an increased mortality from cardiovascular disease in patients taking tolbutamine with diabetes was noted in the University Group Diabetes Study.[5] There are no long-term trials evaluating cardiovascular outcomes or mortality in patients receiving meglitinide therapy, and whether these agents are associated with adverse outcomes following a myocardial infarction is not known at this time.[1]
- Overall, meglitinides are effective in decreasing glycosylated hemoglobin (HbA_{1c}), fasting plasma glucose, and postprandial glucose in patients with type 2 diabetes mellitus.
- Data from limited head-to-head clinical trials, suggest that repaglinide results in greater reductions in HbA_{1c} and fasting plasma glucose levels compared to nateglinide.[6-28]

Key Points within the Medication Class

- According to current clinical guidelines:
  - Metformin remains the cornerstone of most antidiabetic treatment regimens.
  - Patients with a high HbA_{1c} will most likely require combination or triple therapy in order to achieve glycemic goals. At this time, uniform recommendations on the best agent to be combined with metformin cannot be made; therefore, advantages and disadvantages of specific antidiabetic agents for each patient should be considered.
  - The meglitinides are recommended as a potential second line treatment option to be added to or used in combination with metformin in patients not achieving glycemic goals.
  - Patients for whom initial therapy with metformin is not appropriate may be initiated on another oral antidiabetic agent, such as a sulfonylurea/meglitinide, pioglitazone, or a dipeptidyl peptidase-4 inhibitor, and in occasional cases where weight loss is seen as an essential aspect of therapy, initial therapy with an incretin mimetic may be useful.
  - In addition, guidelines recognize the potential use of meglitinides when postprandial hyperglycemia is present.
  - Among all current clinical guidelines, preference of one meglitinide over another is not stated.[29-34]
- Other Key Facts:
  - Nateglinide is the only meglitinide that is available generically.

References

1. McCulloch DK. Sulfonylureas and meglitinides in the treatment of diabetes mellitus. In: Basow DS (Ed). UpToDate [database on the internet]. Waltham (MA): UpToDate; 2013 [cited 2013 Apr 25]. Available from: http://www.utdol.com/utd/index.do.
2. Starlix® [package insert]. East Hanover (NJ): Novartis Pharmaceuticals Corporation; 2013 Jan.
3. Prandin® [package insert]. Princeton (NJ): Novo Nordisk Inc.; 2012 Mar.
4. PrandiMet® [package insert]. Princeton (NJ): Novo Nordisk Inc; 2012 Apr.
5. No authors listed. A study of the effects of hypoglycemia agents on vascular complications in patients with adult-onset diabetes. IV. Supplementary report on nonfatal events in patients treated with tolbutamine. Diabetes. 1976 Dec;25(12):1129-53.
6. Taki H, Maki T, Iso T, Tanabe S, Kajiura T. Post marketing study of nateglinide in Japan: treatment of medication-naïve patients with type 2 diabetes. Adv Ther. 2005 Nov-Dec;22(6):621-35.
7. Taki H, Maki T, Iso T, Iwamoto K, Kajiura T. Study of nateglinide in Japan: long-term treatment of patients with type 2 diabetes. Adv Ther. 2006 Mar-Apr;23(2):307-24.
8. Ozbek M, Erdogan M, Karadeniz M, Cetinkalp S, Ozgen AG, Saygili F, et al. Preprandial repaglinide decreases exogenous insulin requirements and A1C levels in type 2 diabetic patients taking intensive insulin treatment. Acta Diabetol. 2006 Dec;43(4):148-51.
9. Schwarz SL, Gerich JE, Marcellari A, Jean-Louis L, Purkayastha D, Baron MA. Nateglinide, alone or in combination with metformin, is effective and well tolerated in treatment-naïve elderly patients with type 2 diabetes. Diabetes Obes Metab. 2008;10(8):652-60.
10. Marre M, Van Gaal L, Usadel K-H, Ball M, Whatmough I, Guitard C. Nateglinide improves glycemic control when added to metformin monotherapy: results of a randomized trial with type 2 diabetes patients. Diabetes Obes Metab. 2002;4(3)177-86.
11. Horton E, Clinkingbeard C, Gatlin M, Foley J, Mallows S, Shen S. Nateglinide alone and in combination with metformin improves glycemic control by reducing mealtime glucose levels in type 2 diabetes. Diabetes Care. 2000;23(11):1660-5.
12. Hollander P, Schwartz S, Gatlin M, Haas SJ, Zheng H, Foley JE, et al. Importance of early insulin secretion comparison of nateglinide and glyburide in previously diet-treated patients with type 2 diabetes. Diabetes Care. 2003;24(6):983-8.
13. Fonseca V, Grunberger G, Gupta S, Shen S, Foley JE. Addition of nateglinide to rosiglitazone monotherapy suppresses mealtime hyperglycemia and improved overall glycemic control. Diabetes Care. 2003;26(6):1685-90.
14. Rosenstock J, Hassman D, Madder RD, Brazinsky SA, Farrell J, Khutoryansky N, et al. Repaglinide vs nateglinide monotherapy a randomized, Multicenter study. Diabetes Care. 2004;27(6):1265-70.
15. Li J, Tian H, Li Q, Wang N, Wu T, Liu Y, et al. Improvement of insulin sensitivity and β-cell function by nateglinide and repaglinide in type 2 diabetic patients – a randomized controlled double-blind and double-dummy multicentre clinical trial. Diabetes Obes Metab. 2007;9(4):558-65.
16. Raskin P, Klaff L, Mill J, South SA, Hollander P, Khutoryansky N, et al. Efficacy and safety of combination therapy repaglinide plus metformin vs nateglinide plus metformin. Diabetes Care. 2003;26(7):2063-8.
17. Wang W, Bu R, Su Q, Liu J, Ning G. Randomized study of repaglinide alone and in combination with metformin in Chinese subjects with type 2 diabetes naïve to oral antidiabetes therapy (abstract). Expert Opin Pharmacother. 2011 Dec;12(18):2791-9.
18. Moses R, Slobodniuk R, Boyages S, Colagiuri S, Kidson W, Carter J, et al. Effect of repaglinide addition to metformin monotherapy on glycemic control in patients with type 2 diabetes. Diabetes Care. 1999;22(1):119-24.
19. Civera M, Merchante A, Salvador M, Sanz J, Martínez I. Safety and efficacy of repaglinide in combination with metformin and bedtime NPH insulin as an insulin treatment regimen in type 2 diabetes. Diabetes Res Clin Pract. 2008 Jan;79(1):42-7.

20. Raskin P, Mill J, Saad MF, Cappleman JM, Kaye W, Khutoryansky N, et al. Combination therapy for type 2 diabetes: repaglinide plus rosiglitazone. Diabet Med. 2004;21(4):329-35.
21. Sinnen SG, Dain MP, Mauricio D, DeVries JH, Hoeksra JB, Holleman F. Continuation vs discontinuation of insulin secretagogues when initiating insulin in type 2 diabetes. Diabetes, Obesity and Metabolism. 2010;12:923-5.
22. Black C, Donnelly P, McIntyre L, Royle PL, Shepherd JP, Thomas S. Meglitinide analogs for type 2 diabetes mellitus. Cochrane Database Syst Rev. 2007 Apr 18;(2):CD004654.
23. Gangji AS, Cukierman T, Gerstein HC, et al. A systematic review and meta-analysis of hypoglycemia and cardiovascular events: a comparison of glyburide with other secretagogues and with insulin. Diabetes Care. 2007;30(2):389-94.
24. Monami M, Lamanna C, Marchionni N, Mannucci E. Comparison of different drugs as add-on treatments to metformin in type 2 diabetes: a meta-analysis. Diabetes Res Clin Pract. 208 Feb;79(2):196-203.
25. Kawamori R, Kaku K, Hanafusa T, Katsuhisa I, Kageyama S, Hotta N. Clinical study of repaglinide efficacy and safety in type 2 diabetes mellitus patients with blood glucose levels inadequately controlled by sitagliptin. J Diabetes Investig 2016; 7: 253–259.
26. Bolen S, Feldman L, Vassy J, Wilson L, Yeh HC, Marinopoulos S, et al. Systematic review: comparative effectiveness and safety of oral medications for type 2 diabetes mellitus. Ann Intern Med. 2007 Sep 18;147(6):386-99.
27. Saenz A, Fernandez-Esteban I, Mataix A, Ausejo M, Roque M, Moher D. Metformin monotherapy for type 2 diabetes mellitus. Cochrane Database Syst Rev. 2005 Jul 20;(3):CD002966.
28. Richter B, Bandeira-Echtler E, Bergerhoff K, Clar C, Ebrahim SH. Rosiglitazone for type 2 diabetes mellitus. Cochrane Database Syst Rev. 2007 Jul 18;(3):CD006063.
29. The American Diabetes Association. Standards of medical care in diabetes-2013. Diabetes Care. 2013 Jan;36 Suppl 1:S4-10.
30. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2012 Jun;35(6):1364-79.
31. Qaseem A, Humphrey LL, Sweet DE, Starkey M, Shekelle P; Clinical Guidelines Committee of the American College of Physicians. Oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2012 Feb 7;156(3):218-31.
32. Handelsman Y, Mechanick JI, Blonde L, Grunberger G, Bloomgarden ZT, Bray GA, et al. American Association of Clinical Endocrinologists Medical Guidelines for clinical practice for developing a diabetes mellitus comprehensive care plan: executive summary. Endocr Pract. 2011;17:287-302.
33. Rodboard HW, Jellinger PS, Davidson JA, Einhorn D, Garber AJ, Grunberger G, et al. Statement by an American Association of Clinical Endocrinologists/American College of Endocrinology Consensus Panel on type 2 diabetes mellitus: an algorithm for glycemic control. Endocr Pract. 2009;15(6):541-59.
34. National Institute for Health and Clinical Excellence. Type 2 diabetes: the management of type 2 diabetes. [guideline on the Internet]. London: NICE; 2015 Dec [cited 2016 Jun]. Available from: https://www.nice.org.uk/guidance/ng28.Copeland, K.C., Silverstein, J., Moore, K.R., Prazar, G.E., Raymer, T., Shiffman, R.N., & et al. (2013). Management of newly diagnosed type 2 diabetes mellitus (T2DM) in children and adolescents. Pediatrics 2013;131(2):364-382.