CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213051Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	September 19, 2019
From	Mitra Rauschecker, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # and Supplement#	213051
Applicant	Novo Nordisk
Date of Submission	March 20, 2019
PDUFA Goal Date	September 20, 2019
Proprietary Name	Rybelsus
Established or Proper Name	Semaglutide tablets
Dosage Form(s)	Oral tablets
Applicant Proposed Indication(s)/Population(s)	as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Applicant Proposed Dosing Regimen(s)	Start at 3 mg once daily for 30 days then increase the dose to 7 mg once daily. Dose may be increased to 14 mg once daily if additional glycemic control is needed after at least 30 days on 7 mg
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Recommended Dosing Regimen(s) (if applicable)	Start at 3 mg once daily for 30 days then increase the dose to 7 mg once daily. Dose may be increased to 14 mg once daily if additional glycemic control is needed after at least 30 days on 7 mg

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

Type 2 diabetes mellitus (T2DM) is a serious, chronic medical condition, which has been increasing in prevalence in t
by insulin resistance with insufficient insulin production, and resulting hyperglycemia. Current approved therapies for
like peptide 1 (GLP-1) receptor agonists, which acts to improve glucose dependent insulin secretion, slows gastric em
and postprandial glucagon levels. Semaglutide is a GLP-1 receptor agonist, and the subcutaneous (sq) injectable form
approved as an adjunct to diet and exercise for the treatment of adults with T2DM. The applicant has developed an ora
semaglutide, which would be the first oral GLP-1 receptor agonist, with the same proposed indication as the sq semag

The clinical development program for semaglutide consisted of 33 studies, which included 7 multi-national, phase 3 c
adults with T2DM, along with 2 studies conducted in Japan, and a pre-market CVOT to evaluate cardiovascular safety
demonstrated a dose-dependent reduction in HbA1c, and the maintenance doses (7 and 14 mg) were superior to placeb
(excluding liraglutide). While the reduction in HbA1c compared to placebo was somewhat less for oral semaglutide as
semaglutide based on historical data, oral semaglutide demonstrated substantial evidence of effectiveness for glycemic
well controlled trials, and the oral formulation offers a therapeutic alternative from injectable therapies.

The safety findings for semaglutide were generally consistent with the known safety profile of sq semaglutide. There w
gastrointestinal adverse events versus placebo, specifically nausea and vomiting, which is expected with GLP-1 recept
enhance oral absorption of semaglutide, the applicant used a novel excipient, salcaprozate sodium (SNAC). The noncl
increase in mortality with high dose administration of SNAC, attributed to inhibition of cellular respiration, associated
levels. In the phase 3 clinical studies, there were few events of lactic acidosis overall, with no evidence of an imbalanc
groups. Similarly, serum lactate levels were evaluated in several of the trials, and there was no evidence of increased l
data do not suggest an increased risk of lactic acidosis related to semaglutide/SNAC.

Nonclinical studies to evaluate the safety of the SNAC demonstrated that SNAC concentrated in the milk of lactating
alternative treatment options, including sq semaglutide, breastfeeding is not recommended for oral semaglutide. In add
requirement (PMR) for a milk-only lactation study to assess concentration of semaglutide and SNAC in breast milk is

Diabetic retinopathy was identified as a safety concern during the development program for sq semaglutide, with an in
retinopathy complications seen in subjects treated with sq semaglutide during the cardiovascular outcomes trial (CVO
diabetic retinopathy complications was attributed to the glucose lowering effect of sq semaglutide, with an early progr
retinopathy with improved glycemic control. For oral semaglutide, diabetic retinopathy events were collected by the a
underwent baseline and end of treatment eye exams, including fundoscopy with dilation. Overall, the data do not sugg

retinopathy events for oral semaglutide, although the trials were not designed to adequately assess the retinopathy risk the trials, and the low risk population. For this reason, I recommend the risk of diabetic retinopathy is included in labe semaglutide.

The applicant also completed a CVOT to assess the cardiovascular safety of semaglutide designed to satisfy the 2008 assessing cardiovascular safety for new therapies intended to treat type 2 diabetes. The trial was event-driven, and acc major adverse cardiovascular events (MACE). The data from this study ruled out a 1.3 risk margin and support that no study should be required to assess the CV safety of semaglutide.

In summary, the clinical development program demonstrated semaglutide has a favorable benefit-risk profile. Semaglu ability to improve glycemic control, and the safety profile is generally consistent with sq semaglutide and with other n analog class. I recommend approval of semaglutide as an adjunct to diet and exercise to improve glycemic control in a mellitus.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusi
Analysis of Condition	• Type 2 diabetes mellitus (T2DM) is a disease characterized by hyperglycemia, insulin resistance, and relative impairment of insulin secretion. • It is a relatively common disease that is estimated to affect approximately 30 million people in the United States as of the 2015 Center for Disease Control report. • T2DM is often associated with other metabolic derangements, such as dyslipidemia, hypertension, and obesity. • Chronic complications of T2DM include cardiovascular disease, retinopathy, nephropathy, and neuropathy.	T2DM is a serious, life can lead to serious m untreated.
Current Treatment Options	• Treatment options for T2DM includes lifestyle modifications, usually followed by the addition of one or multiple different medications. • There are currently multiple classes of pharmacologic treatments for T2DM, including biguanides, sulfonylureas, insulin and insulin analogs, glucagon-like peptide-1 (GLP-1) analogs, dipeptidyl peptidase-4 (DPP4) inhibitors, and sodium-glucose linked transporter (SGLT)-2 inhibitors.	There are multiple dif for patients with T2D

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Dimension	Evidence and Uncertainties	Conclusi
	• Semaglutide is currently approved as a sq formulation. • There are no approved oral GLP-1 receptor agonists.	
Benefit	• Semaglutide demonstrated efficacy in reducing HbA1c in a dose-dependent manner, with an approximate reduction in HbA1c of 0.8-1.1% compared to placebo. • Semaglutide also resulted in weight loss of approximately -1 to -4 kg compared to placebo. • Semaglutide is an oral formulation, which would allow use in patients who cannot or prefer not to use injectable semaglutide.	Semaglutide was effe control, and also resu weight.
Risk and Risk Management	• The most common adverse events were gastrointestinal events. • Safety concerns common to all GLP-1 receptor agonists include pancreatitis, medullary thyroid tumors, and acute kidney injury. The development program for semaglutide did not change these concerns, or raise any new safety concerns. • There was no evidence of increased cardiovascular risk. • There was no evidence for increase in lactic acidosis events related to SNAC. Nonclinical studies demonstrated SNAC concentrated in the milk of lactating animals. • There was no evidence of increase in diabetic retinopathy complications.	The safety profile for generally consistent w other GLP-1 receptor with semaglutide can communicated with la recommended to asse semaglutide/SNAC co

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