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APPLICATION NUMBER:

209637Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	(see electronic signature)
From	William H. Chong
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 209637
Applicant	Novo Nordisk Inc.
Date of Submission	December 5, 2016
PDUFA Goal Date	December 5, 2017
Proprietary Name / Non-Proprietary Name	OZEMPIC (semaglutide)
Dosage form(s) / Strength(s)	Once weekly subcutaneous injection (0.5 mg, or 1 mg)
Applicant Proposed Indication(s)/Population(s)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Recommendation on Regulatory Action	*Approval*
Recommended Indication(s)/Population(s) (if applicable)	*Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus*

Review Team:

Drug Substance Reviewer	Joseph Leginus
Drug Product Reviewer	Muthukumar Ramaswamy
Quality Microbiology Reviewer	Elizabeth Bearr
Quality Process Reviewer	Chaoying Ma
Facilities Reviewers	Vidya Pai (CDER) and Christopher Brown (CDRH)
Quality Technical Lead	Suong Tran
Nonclinical Reviewer	Federica Basso
Carcinogenicity Statistics Reviewer (DB-VI)	Hepei Chen
QT-IRT	Janell Chen
Clinical Pharmacology Reviewers	Shalini Wickramaratne Senarath Yapa and Justin Earp
Clinical Reviewer	Andreea Lungu
Efficacy Statistics Reviewer (DB-II)	Jiwei He
Safety Statistics (DB-VII)	Ya-Hui Hsueh
DMEPA Reviewer	Susan Rimmel
CDRH/GHDB Consultant	Sarah Mollo
Immunogenicity	Mohanraj Manangeeswaran
DPMH Reviewer	Jane Liedtka
DRISK Reviewer	Till Olickal
DMPP Reviewer	Sharon Williams
OPDP Reviewer	Domenic D'Alessandro
Ophthalmology Consultant	Wiley Chambers
Office of Scientific Investigation	Cynthia Kleppinger
Division of Epidemiology	Yandong Qiang
Project Manager	Peter Franks

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Type 2 diabetes mellitus (T2DM) is a condition of chronic impaired glucose homeostasis that results in chronic hyperg risk for microvascular and macrovascular complications. Therapies for T2DM have focused on improving glycemic c change in hemoglobin A1c (HbA1c), as better glycemic control has been correlated with better clinical outcomes. Wh products approved both as individual drugs and as fixed combination drug products (FCDP), many patients are unable Thus, patients and prescribers have been advocating for additional therapeutic options to facilitate individualization of will improve patients' ability to achieve glycemic control.

Semaglutide is a once weekly glucagon-like peptide-1 (GLP-1) receptor agonist that has been developed as an adjunct improve glycemic control in adults with type 2 diabetes mellitus (T2DM). In controlled clinical trials, use of semaglu weekly resulted reduction in HbA1c (treatment difference compared to placebo of -1.1% to -1.6% at 30 weeks). Addi be desirable for patients include a reduction in body weight (treatment difference compared to placebo of -2.2 to -4.7 k

Safety findings from the semaglutide development program were generally consistent with what would be expected fo receptor agonist. The most common adverse reactions are nausea and vomiting. The inherent risk for hypoglycemia v be low, but this is increased when co-administered with insulin (and likely to be increased when co-administered with as sulfonylureas). While no difference in the incidence of pancreatitis was seen in the development program, patients had increases in serum amylase and lipase. No notable difference in malignancies (including for medullary thyroid ca development program, but duration of exposure was relatively short and may not be sufficient to fully exclude an incr findings support that the concern for MTC with long-acting GLP-1 receptor agonists also applies to semaglutide. As a expected that semaglutide will carry some risk for anti-semaglutide antibody formation and hypersensitivity reactions. and titer of anti-semaglutide antibodies was relatively low, and no apparent increased risk for clinically significant hyp seen.

In support of the semaglutide new drug application (NDA), the applicant has also completed a cardiovascular outcome exclude excess cardiovascular risk. This trial ran for two years and accrued a total of 254 first major adverse cardiova Based on this trial, the applicant has adequately established that there is no excess cardiovascular risk with semaglutid

An unexpected finding from the CVOT was an increased risk for diabetic retinopathy complications. This was seen ea increased risk persisted through the two-year observation period of the trial. The patients at greatest risk were those w

baseline. Though the definitions and means by which events were identified were considered inadequate had the appl
indication of reduced risk for diabetic retinopathy progression, the finding is nevertheless concerning given that impro
expected to reduce the risk for complications of diabetes. The applicant has posited that this finding is a result of the g
semaglutide and that it is consistent with what would be expected based on findings from other large clinical trials (i.e
Complications Trial [DCCT]). While adjusting for change in HbA1c does attenuate the observed hazard ratio, it may
observed finding. The FDA ophthalmology consultant acknowledged that the finding does raise some concerns, but th
be expected and that it does not adversely impact the benefit-risk. A public Advisory Committee meeting was conven
and risks of semaglutide, including the diabetic retinopathy findings. The external ophthalmology experts and other A
members expressed opinions similar to that of the FDA ophthalmology consultant.

The finding of increased risk for diabetic retinopathy complications is concerning, but I do not believe it results in an u
Diabetic retinopathy is but one of several diabetic complications that is expected to be favorably impacted by improve
from the semaglutide development program have not suggested that these other clinical outcomes are similarly advers
the data on semaglutide for diabetic retinopathy complications are limited. The longest exposure to semaglutide was t
that in the DCCT there was an early worsening of diabetic retinopathy progression with intense glycemic control whic
approximately three years. Whether longer term treatment with semaglutide would similarly result in a reduced risk o
progression is unknown, but it may not be feasible or ethical to conduct such a study. While this uncertainty remains,
diabetic retinopathy can be monitored and that there are effective therapies to treat it such that serious adverse clinical
can be avoided with proper ophthalmologic care. The patients at greatest risk were those with diabetic retinopathy at l
would generally be expected to have closer ophthalmology follow-up.

In summary, I believe that semaglutide has a favorable benefit-risk profile. The findings from the development progra
of semaglutide to improve glycemic control, and the safety profile is generally consistent with other member of the cla
cardiovascular safety of semaglutide has been adequately established. Though there was a finding for increased risk o
complications, I do not believe that it is so substantial as to outweigh the benefits. While the finding raises some ques
semaglutide with respect to reducing the risk for diabetic retinopathy progression, improved glycemic control should c
other diabetic complications (e.g., diabetic nephropathy, diabetic neuropathy). Further, diabetic retinopathy can be mo
prevent serious clinical outcomes (e.g., blindness).

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