Assessment Report for Pharmaceutical Medicinal Products
Marketing Authorization Application for Invokana®
Dated 26 April 2017
Prepared By
Division of Health Product Business Promotion
Food and Drug Administration, Ministry of Public Health

Name of product	Invokana®
Active substance(s)	INN: Canagliflozin
Pharmaceutical form	Film-coated tablets
Strength(s)	100 mg and 300 mg
Route(s) of administration	Oral administration
Therapeutic indication(s)	**Indication as stated in patient information leaflet:** INVOKANA is a prescription medicine used along with diet and exercise to lower blood sugar in adults with type 2 diabetes.
	Indication according to SmPC: INVOKANA is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Limitation of Use Invokana is not recommended in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis
Application number and date of receipt	1C 15008/60 (N) and 1C 15009/60 (N) 26 April 2017
E-Identifier number	E5900018

Table of Contents

	Page
Part 1: Introduction and Summary Review	**4**
Part 2: Summary of the Dossier	**5**
2.1 Type of Marketing Authorization Applications	**5**
2.2 Administrative Data	**5**
2.2.1 Product	**5**
2.2.2 Source	**5**
Part 3: Analytical Physico-Chemical, Biological, and Microbiological Documentation	**6**
3.1 Drug Substance	**6**
3.1.1 Manufacture	**6**
3.1.2 Control of Drug Material	**6**
3.1.3 Container Closure System	**6**
3.1.4 Stability	**6**
3.2 Drug Product	**6**
3.2.1 Manufacture	**6**
3.2.2 Process	**7**
3.2.3 Qualitative and Quantitative Particulars of the Constituents	**7**
3.2.4 Control of Drug Product	**7**
3.2.5 Container Closure System	**7**
3.2.6 Stability	**8**
Assessor's Conclusions on Quality	**8**
Part 4: Non-clinical Documentation	**8**
Part 5: Clinical Study Reports	**9**
Assessment on Drug Labels	**11**
Assessment on Consumer Information Leaflet	**12**
Assessment on Leaflet for Healthcare Professionals	**12**
Part 6: Overall Benefit/Risk Assessment	**13**
References	**14**
Appendices	

Explanation of Symbols and Abbreviations

ADA Guideline	American Diabetes Association Guideline
HbA1c	Hemoglobin A1c
DPP-4 inhibitor	Dipeptidyl peptidase-4 inhibitor
SGLT2 inhibitor	Sodium-glucose co-transporter-2 inhibitor
GLP-1 receptor agonist	Glucagon-like peptide-1 receptor agonist
RTG	Renal Threshold for Glucose
EMA	European Medicines Agency

Assessment Report for Pharmaceutical Medicinal Products
Marketing Authorization Applications for Invokana® 100 mg and 300mg
Application Numbers: 1C 15008/60 (N), 1C 15009/60 (N)
E-identifier: e5900018
(Manufacturing Site: Janssen-Cilag S.p.A., Borgo San Michele, Latina, Italy)
Dated 26 April 2017

Part 1: Introduction and Summary Review

The results from a Thai people's health survey by physical examination demonstrated that the prevalence of diabetes/having abnormal blood sugar levels in the population aged 15 years old and over was 6.9 percent in 2009 and increased to 8.96 percent in 2014[1]

The ADA guideline 2017[2] suggests that patients with type 2 diabetes (a condition in which the pancreatic beta cells have lost their ability to secrete insulin, including the condition in which cells are resistant to insulin) are classified according to their HbA1c levels, and those groups are treated accordingly, starting from diet in conjunction with exercise. If unable to control the sugar levels, the treatment should then begin with metformin as the first drug owing to its good efficacy, low cost, and less side effects. In the case that metformin cannot be used due to contraindications or because the sugar levels cannot be controlled with metformin alone, the ADA recommendations[2] suggest the use of drugs in other classes as either a substitute or an adjunct. The drug classes recommended to be used instead of or in combination with metformin include sulfonylureas, thiazolidinediones, DPP-4 inhibitors, SGLT2 inhibitors, GLP-1 receptor agonists, or insulin (basal). If still unable to control the sugar levels, the treating physician can prescribe the third medication to better control the patient's sugar levels, and those drugs in the above-mentioned classes are still recommended. Therefore, patients with type 2 diabetes can use a variety of drugs to control their sugar levels to meet the glycemic target. For this reason, it is a goal to develop new drugs to improve glycemic control in these patients.

Canagliflozin Is a drug in the class of SGLT2 inhibitors with a mechanism for blood sugar reduction through interferences with the SGLT-2 protein, which functions to reabsorb sugar from the blood filtered in the proximal tubule and helps maintain blood sugar levels. The inhibition of this SGLT-2 protein results in increased urinary glucose excretion and reduced threshold for glucose reabsorption in the kidneys (Renal Threshold for Glucose or RTG), thereby lowering blood sugar levels. The plasma glucose concentration decreases regardless of the insulin levels. Osmotic diuresis occurs, causing a decrease in the systolic blood pressure and weight reduction from the loss of energy supplied by glucose.

In Thailand, Invokana received marketing authorization on 7 April 2015 with the marketing authorization numbers of 1C 36/58 (NC) for the 100 mg strength and 1C 37/58 (NC) for the 300 mg strength. In the marketing authorization assessment, the clinical data have already been reviewed. Later, the company wished to add a manufacturing site abroad, and thus, submitted marketing authorization applications for Invokana 100 mg and Invokana 300 mg with the application numbers of 1C 15008/60 (N) and 1C 15009/60 (N), respectively, dated 26 April 2017, E-identifier: e5900018, dated 31 August 2016. In this regard, they requested to refer to the original clinical study data in conjunction with the reports on further conducted clinical studies, including those related to the effects of Invokana usage on cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke, as well as pharmacovigilance studies by monitoring adverse events. The results from these studies indicated that Invokana did not cause an increased risk of heart disease, but significantly expanded the risk of lower limb amputations (hazard ratio, 1.97; 95% CI, 1.41-2.75), for which the USFDA has warned of such incidence in the leaflet.

Invokana is one of the options used for glycemic control in adults with type 2 diabetes, with clinical studies showing its efficacy and safety when using either as a single drug or in combination with other drugs. It has received marketing authorization in over 60 countries worldwide, including those in the Americas, Europe, Australia, Asia, as well as Thailand.

Based on the summary of the expert resolution on marketing authorization assessment, it can be concluded that Invokana preparation with manufacturing site addition is acceptable in terms of both quality and safety. When comparing benefits and risks, it was found that the benefits of Invokana preparation outweigh the risks so it is acceptable.

Part 2: Summary of the Dossier

2.1 Type of Marketing Authorization Applications

- **Product type**: Modern drug for humans with new chemical entities
- **Application type**: Variation applications with major variation, in which the data on the quality and the clinical trials further conducted on their own product were submitted for consideration.
- **Review method**: Abbreviated assessment due to the availability of an un-redacted evaluation report from stringent NRAs recognized by Thai FDA, *i.e.*, the EMA, together with the academic expert meeting for marketing authorization assessment on 27 November 2017.

2.2 Administrative Data

2.2.1 Product

Name of product: invented name	Invokana®
Active substance(s)	Canagliflozin
Strength(s)	100 mg and 300 mg
Pharmaco-therapeutic group (EMA)/Therapeutic class (USFDA)	Sodium-glucose co-transporter 2 (SGLT2) inhibitors ATC code: A10BK02
Pharmaceutical form	Film-coated tablets
Route of administration	Oral
Drug Characteristics	Invokana (100 mg film-coated tablets): Yellow, capsule-shaped tablet, debossed with "CFZ" on one side and "100" on the other side Invokana (300 mg film-coated tablets): White to off-white, capsule-shaped tablet debossed with "CFZ" on one side and "300" on the other side
Packaging	PVC/Alu blisters
Package size(s)	PVC/Alu blisters with 10 tablets each, which are then packed in a paperboard carton with 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 blister strips

2.2.2 Source

- **Name and address of the applicant for importation**
  106 Moo 4, Lad Krabang Industrial Estate, Chalongkrung Road, Lamplatew, Lad Krabang, Bangkok 10520
- **Name and address of the manufacturer(s) of the dosage form**
  Janssen- Cilag S.p.A. Via C. Janssen, Borgo San Michele, 04100 Latina, Italy
- **Name and address of the manufacturer(s) responsible for repacking**
  Janssen-Cilag S.p.A. Via C. Janssen, Borgo San Michele, 04100 Latina, Italy
- **Name and address of the manufacturer(s) responsible for commercial batch release**
  Janssen-Cilag S.p.A. Via C. Janssen, Borgo San Michele, 04100 Latina, Italy
- **Name and address of the manufacturer(s) responsible for secondary packaging**
  Janssen-Cilag S.p.A. Via C. Janssen, Borgo San Michele, 04100 Latina, Italy

Assessment

Janssen-Cilag Ltd. wished to submit marketing authorization applications for Invokana 100 mg and Invokana 300 mg with another dosage form manufacturing site in addition to Janssen Ortho, LLC,

Gurabo, Puerto Rico (while the manufacturing site for secondary packaging and commercial batch release is Janssen-Cilag S.p.A., Latina, Italy), as listed in the granted marketing authorization. Therefore, the company submitted the marketing authorization applications for Invokana 100 mg and Invokana 300 mg, which will also be manufactured by Janssen-Cilag S.p.A., Latina, Italy, as an eCTD with the e-identifier number of e5900018.

The marketing authorization assessment revealed that Janssen-Cilag S.p.A., Latina, Italy, is a dosage form manufacturing site licensed for the production of non-sterile products, repacking, and analysis. It has been certified for good manufacturing practice for non-sterile products in accordance with the PIC/S standards recognized in Thailand. A certificate of GMP compliance of a manufacturer issued in Italy is also available.

Part 3: Analytical Physico-Chemical, Biological, and Microbiological Documentation

3.1 Drug Substance

3.1.1 Manufacture

The active substance manufacturer is Janssen Pharmaceutica NV, Janssen Pharmaceuticalaan 3, B-2440 Geel, Belgium, which is the active substance manufacturer listed in their original marketing authorization granted in 2015. A certificate of GMP compliance of a manufacturer issued in Belgium, which is among the PIC/S member countries, is still valid. The manufacturing process involves organic synthesis reactions and purification steps.

3.1.2 Control of Drug Material

For the control of starting materials in the production of canagliflozin active substance, they are tested as per standards, and specifications have been established. In addition, their purity is appropriately determined. Based on the analysis results, the standard requirements for active substances were achieved**.**

3.1.3 Container Closure System

Canagliflozin is packed in a suitable container, and the manufacturer has already presented such information.

3.1.4 Stability

Stability testing of materials is performed in every step considered suitable and consistent with the ICH guidelines, which also provide the test conditions appropriate for the manufacturing country.

3.2 Drug Product

3.2.1 Manufacture

3.2.1.1 Manufacturing Site Addition With Changes in the Manufacturing Procedure, Except for Batch Release, Batch Control, Primary and Secondary Packaging for Non-sterile Products ((B.II.b.1.e) IB: MaV-4)

Janssen-Cilag Ltd. wished to submit marketing authorization applications for Invokana 100 mg and Invokana 300 mg with another dosage form manufacturing site in addition to Janssen Ortho, LLC, Gurabo, Puerto Rico, as listed in the granted marketing authorization, thereby requesting an approval of the production by Janssen-Cilag S.p.A., Latina, Italy. Furthermore, Janssen-Cilag Ltd. has submitted a letter certifying that various production records from this new manufacturing site are in accordance with the request submitted for marketing authorization amendments in the EU in all respects.

3.2.1.2 Change in the Address of the Manufacturing Site ((A.5.a) Iain: MiV-N4)

The dosage form manufacturer has notified the change of the postal code of the new manufacturing site from Janssen-Cilag S.p.A., Latina, Italy 04010 to Janssen-Cilag S.p.A., Latina, Italy 04100. From the information and documents assessed by the EMA, this information is confirmed to be correct. Janssen-Cilag S.p.A., Latina, Italy, is a dosage form manufacturing site licensed for the production of non-sterile products, repacking, and analysis. It has been certified for good manufacturing practice recognized in Thailand for non-sterile products. A certificate of GMP compliance of a manufacturer issued in Italy, which is among the PIC/S member countries, is also available.

3.2.2 Process

3.2.2.1 Batch Size

Since the addition of a manufacturing site in Latina requires some changes in equipment, the batch size needs to be adjusted accordingly.

3.2.2.2 Minor Change in the Manufacturing Process ((B.II.b.3.z) IB: MiV-PA20)

The manufacturing procedure for Invokana has been previously approved for the production by the original manufacturing site, which is Janssen Ortho, LLC, state Road 933. Km 0.1, Mamey Ward, Gurabo, Puerto Rico 00778, USA. In the current marketing authorization applications, the product is manufactured by Janssen-Cilag S.p.A., Latina, Italy, and there are some changes in the manufacturing procedure that slightly affect the quality. The marketing authorization assessment by the EU also revealed no effects on the quality.

3.2.2.3 Process Validation

In the e-submission, Janssen-Cilag Ltd. provided the process validation data both from the original manufacturing site, which is Janssen Ortho, LLC Gurabo, Puerto Rico, USA, and from Janssen-Cilag S.p.A., Latina, Italy. It was found that both manufacturing sites can control their production to meet the established specifications.

Furthermore, the manufacturer has prepared a method validation report that has been verified by the Analytical and Pharmaceutical Development Centre in India, which is one of trustworthy sites and has been certified by Janssen's Pharmaceutical Development & Manufacturing Sciences (PDMS) for validation. From the report, it was found that various methods are effective as per the method validation criteria and can control the products to meet the established specifications.

3.2.3 Qualitative and Quantitative Particulars of the Constituents

The formula is appropriate and the constituents are adequately tested for quality and standards.

3.2.4 Control of Drug Product

Canagliflozin quality assessment based on batch analysis by Janssen-Cilag S.p.A., Latina, Italy, and Janssen Ortho, LLC Gurabo, Puerto Rico, USA, revealed that both the 100 mg and 300 mg strengths met the acceptance criteria. When considering the solubility data, the established standard criteria were also met. These findings demonstrated that manufacturing site addition and slight modifications of the manufacturing procedure did not affect the quality control and production of this drug substance.

3.2.5 Container Closure System

Invokana 100 mg and Invokana 300 mg are packed in the primary packaging in the form of polyvinylchloride (PVC)/aluminum blisters, consisting of 10mil PVC thermoforming film and aluminum foil with heat seal coating. These materials conform to the European standards such

that they can be used for food packaging. The blisters will then be packed in the secondary packaging, which is a paperboard carton for transportation.

The manufacturer requested to change the specifications of the primary packaging, which meets the standards appropriate for drug packaging. Packaging quality assessment based on the certificate of analysis of packaging materials indicated that the acceptance criteria were met as per the packaging specifications.

3.2.6 Stability

From the stability data for 3 batches of Invokana 100 mg and Invokana 300 mg, the results from physical and biological studies for 36 months under long term conditions (5°C, 25°C/60% RH, and 30°C/75% RH), 6 months under accelerated conditions (40°C/75% RH), and 3 months at 50°C, as well as the photostability study according to the ICH guidance, are provided.

The product stability data submitted by the company for marketing authorization applications demonstrated the stability of the finished product manufactured by the Gurabo site when using the drug substance manufactured via a commercial production method. The company requested to refer to this information as the stability data of the product manufactured by the new Latina site because a similar manufacturing process was used. The company will later submit the ICH-compliant product stability data for the product manufactured with the drug substance synthesized using the same method by the Latina site. Based on the data received for both the long-term and accelerated studies on the product manufactured by the original site, neither changes nor trends to fall out of specifications were observed, and the product is stable for a period of 24 months.

Assessment

The stability of the drug product from the Gurabo site is appropriate and consistent with the ICH guideline when stored at 30°C/75% RH. The shelf-life is 24 months. The company requested to refer to these study results as the stability study results for the finished product manufactured by the Latina site using a similar production method. They will later submit the ICH-compliant stability study data for the finished product manufactured by the Latina site, as specified in their affirmative.

Assessor's Conclusions on Quality

Based on a comprehensive analysis of the Type IB variation report, as well as the acknowledgment of receipt and review outcome of type IA variations to the terms of the marketing authorization (un-redacted assessment report) by the European Medicines Agency and the public assessment report from the European Union, along with additional analysis based on the context and regulations of Thailand/ASEAN, it was found that the production and quality control of the drug substance and drug product are appropriate and comply with reliable standards. The company will later submit the ICH-compliant stability study data for the finished product manufactured by the new Latina site, and such condition is specified in their affirmative.

Part 4: Non-clinical Documentation

Invokana received marketing authorization on 7 April 2015 with the marketing authorization numbers of 1C 36/58(NC) for the 100 mg strength and 1C 37/58 (NC) for the 300 mg strength. The expert panel responsible for marketing authorization assessment has already reviewed the data from *in vitro* or animal studies. In the current applications, the company therefore requested to refer to those original study data.

Assessment

The assessment of preclinical documents is acceptable since only the manufacturing site has been changed, and it is not different from the original site. Therefore, the data from the marketing authorization for the original manufacturing site can be referred.

Part 5: Clinical Study Reports

Invokana received marketing authorization on 7 April 2015 with the marketing authorization numbers of 1C 36/58 (NC) for the 100 mg strength and 1C 37/58 (NC) for the 300 mg strength for the indication of blood sugar reduction in adults with type 2 diabetes when using either as a single drug or an adjunct to the other medications prescribed for blood sugar reduction. The expert panel responsible for marketing authorization assessment has already reviewed the data from clinical studies. In the current applications, the company therefore requested to refer to those original study data, in conjunction with the results from recently completed clinical studies. The supporting information is presented in the table below for the clinical trials on Invokana.

Table 1 Clinical trial on Invokana (Canagliflozin)

No.	Author/ Year	Study Place	Design	Subjects/ Primary Objective(s)	Intervention	Outcome
1	Bruce Neal, Vlado Perkovic, Kenneth W. Mahaffey, et al./ June, 2017.	Phase IV in 667 centers over 30 countries.	The integrated analysis of CANVAS and CANVAS-R trials. (double-blind, randomized, placebo-controlled trial)	10,142 participants with type 2 diabetes and high cardiovascular risk. **Primary outcome**: composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.	**CANVAS Program (CANVAS+ CANVAS-R)** **Control group:**: (n = 4347) **Treatment group:** (n = 5795) **CANVAS** Participants were randomly assigned in a 1:1:1 ratio to receive Canagliflozin at a dose of 300 mg, Canagliflozin at a dose of 100 mg, or matching placebo. **CANVAS-R** Participants were randomly assigned in a 1:1 ratio to receive Canagliflozin, administered at an initial dose of 100 mg daily with an optional increase to 300 mg starting from week 13, or matching placebo.	primary outcome: - The composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke hazard ratio, 0.86; 95% [CI], 0.75 to 0.97; P<.001 for non-inferiority; P = 0.02 for superiority). - The renal outcomes are not statistically significant. - The progression of albuminuria (hazard ratio, 0.73; 95% CI, 0.67 to 0.79) - The composite outcome of a sustained 40% reduction in the eGFR, the need for renal-replacement therapy, or death from renal causes (hazard ratio, 0.60; 95% CI, 0.47 to 0.77). Adverse reactions: - Increased risk of amputation hazard ratio, 1.97; 95% CI, 1.41- 2.75 (amputations were primarily at the level of the toe or metatarsal)

Assessment

Based on a comprehensive analysis of the data above, together with the original clinical study data assessed in the marketing authorization granted on 7 April 2015 for Invokana 100 mg and Invokana 300 mg with the marketing authorization numbers of 1C 36/58 (NC) and 1C 37/58 (NC), respectively, it was found that the same indication for blood sugar reduction in adults with type 2 diabetes when using either as a single drug or in combination with other medications prescribed for blood sugar reduction, along with diet and exercise as suggested by the physician, is still applicable. However, since the above-mentioned studies revealed a significant increase in the incidence of the side effects associated with foot or leg amputations, the company should therefore specify in the leaflet about the precautions to be taken to prevent possible occurrence of such conditions. This has already been implemented by Janssen-Cilag Ltd.

Assessment on Drug Labels

Drug Labels

The drug labels prepared by Janssen-Cilag Ltd. in the marketing authorization applications are classified as unit carton label and blister/strip label, with the details in accordance with standard criteria (Thai FDA 2009) in Appendix 3 entitled "Preparation of Drug Labels and Leaflets for Marketing Authorization Applications as per ASEAN Harmonization". They are appropriate and can be summarized as follows.

Unit Carton Label

No.	Topic	Available	Appropriate
1	Trade name	✓	✓
2	Pharmaceutical form	✓	✓
3	Active substance(s)	✓	✓
4	Strength(s)	✓	✓
5	Batch number	✓	✓
6	Manufacturing date	✓	✓
7	Expiration date	✓	✓
8	Drug administration	✓	✓
9	Storage conditions	✓	✓
10	Marketing authorization number	✓	✓
11	Name and address of the licensee	✓	✓
12	Name and address of the manufacturer abroad	✓	✓
13	Special message	✓	✓
14	Recommended dosage (for vitamins and minerals)	n/a	n/a
15	Warnings according to the Notification	✓	✓
16	Package size	✓	✓

✓ Available or appropriate

n/a Not relevant to the evaluated topic

Blister/Strip Label

No.	Topic	Available	Appropriate
1	Trade name	✓	✓
2	Active substance(s) (not to be specified if there are more than 3 active substances)	✓	✓
3	Strength(s) (not to be specified if there are more than 3 active substances)	✓	✓
4	Batch number	✓	✓
5	Expiration date	✓	✓
6	Name/logo of the manufacturer/importer	✓	✓
7	Marketing authorization number (not required)	-	-

8	Additional conditions (such as to be used in health institutions only. If any, they must be specified.)	✓	✓
9	Special message (Not required for small labels with an area not exceeding 3 square inches**)**	-	-

✓ Available or appropriate
n/a Not relevant to the evaluated topic

Assessment on Consumer Information Leaflet

The consumer information leaflet of Invokana (Canagliflozin 100 mg and 300 mg) in Thai as proposed by the licensee has been translated from the USFDA's package leaflet with the same content as that approved by the USFDA. The assessment revealed that the leaflet contains accurate and complete information. It is consistent with the leaflet for healthcare professionals, as well as the assessment of the quality, preclinical, and clinical documents. The main points for patients to follow while taking this drug are summarized, but user testing in Thai people should be performed according to the Notification of the Food and Drug Administration entitled "Guidelines for Leaflet Preparation 2013". Therefore, a condition has been stipulated for the licensee to perform user testing on the approved consumer information leaflet within 12 months after receiving the marketing authorization certificate.

Assessment on Leaflet for Healthcare Professionals

The assessment on the English version of the leaflet for healthcare professionals indicated that the summarized information is consistent with the results from the product quality, preclinical, and clinical studies. The key information that healthcare professionals should know in order for correct and rational drug usage has been summarized.

Part 6: Overall Benefit/Risk Assessment

From the marketing authorization assessment on the quality and clinical aspects, the assessors have analyzed the assessment by EMA along with academic data and literature. It can be concluded that the formula, manufacturing process, and quality control of Invokana preparation are reliable. It is effective and safe for the following indication

INVOKANA is a sodium-glucose co-transporter 2 (SGLT2) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Limitation of Use Invokana is not recommended in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis

While its benefits outweigh the risks, it must be used under the supervision of medical specialists. Therefore, we agree with an approval of marketing authorization with the conditions as specified in the affirmative acknowledged and signed by the company.

Assessor

(Mr. Kridiphol Janthranant, R.Ph.)

Assessor

(Ms. Worasuda Yoongthong, R.Ph.)

References

1. นพ.อรรถเกียรติ กาญจนพิบูลวงศ์, ดร.ภญ.ธนพันธ์ สุขสอาด. รายงานสถานการณ์โรค NCDs "Kick off the goals" ฉบับที่ 2. กระทรวงสาธารณสุข, editor.: The colorsleeper; 2015.

2. William T. Cefalu GB, Lawrence Blonde, Andrew J.M. boulton, David D'Alessio, Mary de Groot, Eddie L. Greene, Frank B. Hu, Steven E. Kahn, Derek LeRoith, Robert G. Moses, Stephen Rich, Matthew C. Riddle, Julio Rosenstock, William V. Tamborlane, Katie Weinger, Judith Wylie-Rosett. . Standards of medical care in diabetes-2017. diabetes care: The journal of clinical and applied research and education 2017;40.