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RESEARCH ARTICLE

The relative bioavailability of two formulations containing 10 mg Dapagliflozin assessed under fasting conditions in a randomized crossover study in healthy Caucasian subjects

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Objective: The aim of the present study was to evaluate the relative bioavailability of two formulations containing 10 mg dapagliflozin in healthy Caucasian subjects under fasting conditions. **Materials and Methods**: Forty-eight healthy Caucasian subjects were enrolled in a single-dose, crossover, balanced, open label, randomized clinical trial, with two treatment, two periods and two sequences. The wash-out period was of 7 days and thirty-eight subjects completed both study periods. Each subject received a single dose of 10 mg dapagliflozin as the reference product Farxiga® (AstraZeneca Pharmaceuticals LP, USA) and the test product developed by Sun Pharmaceutical Industries, India. Dapagliflozin plasma levels were determined from blood samples collected in both study periods before and after dosing until 48 hours by using a validated LC-MS/MS method. For pharmacokinetic analysis of data, the non-compartmental method was used (Phoenix® WinNonlin 6.3). The statistical analysis was performed by SAS software 9.1.3 for the logarithmically transformed values of maximum plasma concentration and area under the curve. **Results**: The 90% confidence intervals for the evaluated pharmacokinetic parameters were found to be in the accepted interval for bioequivalence (80.00-125.00%). **Conclusion**: The 10 mg dapagliflozin immediate release tablet newly developed by Sun Pharmaceutical Industries, India, is bioequivalent with the reference product Farxiga® under fasted state of the subjects.

Keywords: dapagliflozin, bioequivalence trial, Caucasian subjects, fasted state

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Introduction

Bioequivalence and bioavailability studies are fundamental as their purpose is to establish if a newly developed formulation (test formulation) can be interchangeable with a formulation that is already authorized for marketing (reference formulation) [1,2].

In order to establish that the new tested formulation is safe and has the same efficacy as the reference product the manufacturer has to consider a bioequivalence study in which both products are compared after being administered to healthy adult human subjects [3].

The plasma concentration time curve is used to assess the bioavailability of two products and is usually correlated with the rate and extent of absorption. The most important pharmacokinetic parameters that describe the absorption proportion of the active ingredient from the pharmaceutical form are area under the curve (AUC), maximum plasma concentration (C_{max}), and time to reach C_{max} (t_{max}) [4].

The generic products that are proved to have the same qualitative and quantitative composition as the original product are gaining a substantial part of the pharmaceutical market as their substitution with the reference product reduces the costs of treatment for patients [1,3,4].

The bioequivalence study should have a standardized design and subjects included in the study should undergo the same conditions, except the two formulations that are compared, in order to reduce the variability of any factors involved such as food/water intake, exercise, time of administration of the investigational medicinal product (IMP) etc [5,6].

The incidence of Diabetes Mellitus (DM) has increased during the last century and became the most common metabolic condition in the world. Based on the clinical data from International Diabetes Federation in 2017 more than 425 million adults worldwide were known to be diagnosed with diabetes and the number is believed to increase up to more than 629 million until 2045 [7,8].

Type 2 diabetes mellitus (T2DM) is found to be the most common among diabetic patients. The specialists describe eight causes that contribute to the pathophysiology of T2DM, namely decreased insulin secretion, increased glucose reabsorption, increased hepatic glucose production, increased lipolysis, increased glucagon secretion, de-

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creased glucose uptake, neurotransmitter dysfunction and decreased incretin effect [9,10]. Therefore, the therapy should target one or more of these metabolic defects and consider at the same time the patient's needs, by developing a patients-centered treatment scheme [8].

Dapagliflozin is a highly selective sodium-glucose cotransporter 2 (SGLT2) inhibitor , administered via oral route [11]. First of his class, dapagliflozin reduces hyperglycemia by inhibiting SGLT2 which is located in the proximal tubule of kidneys and responsible for the reabsorption of glucose [12]. By inhibiting the reabsorption of glucose, the elimination of glucose in the urine increases. Dapagliflozin has proved its benefits in patients diagnosed with T2DM who cannot tolerate the treatment with metformin and, since March 2019, in patients suffering from type 1 diabetes with BMI ≥ 27 kg/m^2 when treatment with insulin does not provide an adequate control of glycaemia [13].

The patients suffering from DM, either type 1 or 2, are generally facing other associated health problems such as dyslipidemia, obesity, high blood pressure or cardiovascular diseases. Therefore, the treatment usually consists of two or more drugs that patients should take daily. The more medication is added to the therapeutic scheme, the more the costs increase [8,9].

On the other hand, a good approach in the treatment of DM consists of a healthy lifestyle that combines diet with exercise and avoids smoking or alcohol intake [8].

Combined with diet and physical exercise dapagliflozin helps to reduce the weight of patients, factor that can highly influence the outcome of the treatment when T2DM is associated with obesity or other cardiovascular risks [10,14].

The objective of this study was to determine and compare the oral bioavailability and pharmacokinetics of two different immediate release formulations containing 10 mg dapagliflozin, after administration in healthy adult human subjects under fasting conditions.

Materials and Methods

Subjects

The clinical bioequivalence study was conducted respecting all the principles defined in the Declaration of Helsinki (Brazil 2013) and the principles from the Guidelines for Good Clinical Practice ICH E6(R2) (CPMP/ICH/135/95). Furthermore, it was applied the draft guidance on generic drug development for Dapagliflozin tablets enunciated by the U.S. Food and Drug Administration [12]. Before initiating the study, the National Agency of Medicine and Medical Devices, Romania, and Bioethics National Committee of the Medicines and Medical Devices, Romania, approved the clinical study protocol. The clinical trial was performed at the Clinical Pharmacology and Pharmacokinetics Department of Terapia SA-Sun Pharma, Romania.

In order to determine the number of subjects needed for this clinical study, the sample size estimation was calculated based on the available in-house and literature data on dapagliflozin using SAS® system for Windows release 9.1.3, SAS Institute Inc., USA. Thus, it was taken into consideration a Test/Reference ratio of 90-110% and an intra-subject coefficient of variation (CV) of approximately 20%. Therefore, to yield a power of 80% to show bioequivalence of the test and reference products, under bioequivalence assumptions, a number of 36 subjects resulted to be sufficient for enrollment. Nonetheless, possible dropouts of the subjects and/or withdrawals were considered, thus 48 subjects were eventually enrolled in this study.

All subjects included in the study had signed the written informed consent and they were carefully instructed with regard to the details of study such as periods schedule, rights, restrictive and obligations and possible side effects of administered drugs.

The complete study program was communicated to volunteers at the time of consent. All subjects included in the study underwent some standardized screening procedures that consisted of physical examination, vital signs measurements (axillary body temperature, sitting blood pressure and radial pulse) and clinical laboratory tests, such as routine blood analysis, urine tests and medical history investigation. Pregnancy tests were done for females at screening, at admission in the Clinical Unit and at the end of the study. Only the healthy subjects who met the inclusion and exclusion criteria and had clinically normal laboratory profiles were accepted in the study.

Study design

The study was designed as a single-dose, crossover, balanced, open label, randomized study with two treatments, two sequences and two periods. In order to prevent the carry-over effect during the two periods of the study, the wash-out time was 7 days calculated based on the applicable regulatory requirements of the FDA Guidance for Industry (5 times the elimination half-life of the given drug) as the elimination half-life ($t_{1/2}$) of dapagliflozin is known to be 12.9 hours [12].

Study drugs

The test product (T) Dapagliflozin tablets 10 mg was developed by Sun Pharmaceutical Industries, India, while the reference product (R) used was Farxiga® immediate release tablets 10 mg manufactured by AstraZeneca Pharmaceuticals LP, Mount Vernon Ireland, for AstraZeneca Pharmaceuticals LP, USA.

Study protocol

A randomization schedule was generated using the SAS® system for Windows release 9.1.3, SAS Institute Inc., USA, in order to randomly assign the subjects to a specific treatment during the two periods of the study. Therefore,

they alternatively received the test product or the reference product during each period of the study.

In both study periods, the IMPs were administered with 240 mL of 20 % glucose solution. In addition, approximately 60 mL of 20% glucose solution was administered every 15 minutes for up to 4 hours after the dose, as indicated by the draft guidance on generic drug development for Dapagliflozin tablets developed by the US-FDA [15]. This was considered for the safety of subjects and to prevent hypoglycaemia due to the mechanism of action of dapagliflozin.

During housing, all meal plans were identical in both periods as to ensure the same conditions for all the subjects and to reduce bias. The water intake was standardized before and after dosing of the IMP in order to reduce the variability in the IMP absorption, hence subjects were allowed to drink water as desired, except for 1 hour before and after drug administration.

The duration of each study period was of approximately 58 hours (from admission, with 10 hours before dosing, until the last sample collection, at 48 hours post dose). The required fasting period before administration of the IMP in each period was ensured by admitting the subjects with 10 hours before dosing in the Clinical Unit of Terapia SA. After admission, no food was allowed until 4 hours after dosing.

Blood sample collection and processing

The sampling schedule for pharmacokinetic analysis was established considering a higher sampling frequency around t_{max} as predicted, in order to generate a more realistic estimation of maximum exposure. The sampling times were the following: predose and at 0.167, 0.33, 0.5, 0.66, 0.83, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8, 10, 12, 18, 24, 30, 36 and 48 hours post-dose in each study period. Blood samples were collected through indwelling cannula or through vein puncture from the forearm vein in vacutainers containing K_3EDTA as anticoagulant. The total volume of blood collected from each subject during the study did not exceed the legal limit for blood donation.

The collection and processing of the samples for the study were done under low light conditions. The collected samples were kept on ice-cold water bath until they were centrifuged under refrigeration for 15 minutes at a speed of 4000 rpm. The temperature of the centrifuge was set at 4ºC and was maintained up to maximum 10°C.

Bioanalytical Analysis

The separated plasma samples were further kept on ice-cold water bath until storage. Dapagliflozin and Dapagliflozin D5 used as internal standard were detected by LC-MS/MS method. The analytical method was validated for precision and accuracy and the following results were obtained: between-run precision was 0.65% to 2.49%, between-run accuracy was 88.79% to 95.10%, within-run precision was 1.12% to 5.64% and within-run accuracy was 89.44% to 94.39%. For the determination of dapagliflozin in plasma it was used a mass spectrometry method in the negative-ion multiple reaction–monitoring mode with m/z transitions of 407.10→329.20. For the internal standard Dapagliflozin D5 the obtained transition was 412.10→334.10.

Sample preparation was performed by solid phase extraction technique. The processed samples were analyzed on Gemini-NX CIS 110A, 3flm, 50x3 mm column using methanol: acetonitrile: water: ammonia solution 25 % (70:10:20:0.1 v/v/v/v) as mobile phase.

The column oven temperature was 40.00ºC ± 1.00ºC and the autosampler temperature was 10.00ºC ± 1.00ºC. The injection volume consisted of 10.00 µL and the run time was 3 minutes.

The retention time range for Dapagliflozin and Dapagliflozin D5 was 0.7 to 1.7 minutes.

For determination of dapagliflozin's peak area was used Analyst software version 1.6.3 and the concentrations of subjects' samples were calculated from the ratios of the peak area.

The calibration curves were found to be linear over plasma dapagliflozin concentration ranges of 1.01 to 352.50 ng/mL.

Pharmacokinetic and Statistical Analysis

For the non-compartmental pharmacokinetic analysis of dapagliflozin was used Phoenix® WinNonlin 6.3 and the calculated parametres were: C_{max}, t_{max}, observed area under the curve (AUC_{0-t}), total area under the curve ($AUC_{0-\infty}$), extrapolated area under the curve ($AUC_{\%\_extrap}$), and half-life time of dapagliflozin ($t_{1/2}$).

The statistical analysis was performed using SAS software version 9.1.3 for the log-transformed PK parameters (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$).

To determine the bioequivalence of the two products, the pharmacokinetic parameters were analyzed using ANOVA for type III square of means. The 90% confidence interval for the ratio of the test and reference product averages (least squares means) were calculated. The log-transformed pharmacokinetic parameters (AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}) were analyzed. From analysis of log-transformed data, the ratio (T/R) of test and reference product averages for parameters C_{max} and AUC_{0-t} with the 90% confidence interval must be between 80% and 125% for bioequivalence.

Safety evaluation

Even though the safety of the subjects was not defined as an objective of this study, the subjects were monitored for adverse events. Safety measurements were carried out during the study and subjects were specifically asked about any adverse reaction after admission in both periods, before each administration of the investigational medicinal products, after dosing and during housing in the Clinical Unit, and at the end of study. From admission until the

last sampling point, a physician was always available in the Clinical Unit.

Results and Discussion

Forty-eight healthy adult Caucasian subjects who met the inclusion and exclusion criteria described in the study protocol were enrolled in the clinical study, out of which 38 completed the study. The admitted subjects were adults, with the ages between 18-45 years, non-vegetarian diet and with a body mass index (BMI) in the range of 18.5 kg/m^2 to 29.0 kg/m^2. The demographic profile of the subjects who completed the study is shown in Table I. From the 38 subjects who finished the study, 12 were females and 26 were males. Their mean age was 29.9 (in the range of 18 – 44 and a SD of ± 7.61) and had a mean weight of 71.83 kg in the range of 50.0 – 100.0 kg (SD ± 12.332). The mean height of the subjects was 173.14 cm (SD± 12.332).

The investigational medicinal products were well tolerated by the study subjects after a single dose administrated under fasting conditions. During the study, the health status of subjects was not threatened and the recorded adverse effects did not cause study withdrawal. At the end of study safety assessment, 13 not serious adverse events were reported (see Table II). The adverse events reported were increased triglycerides, leukocyturia, increased AST, increased total bilirubin, positive nitrites in urine, decreased platelets, and leucocytosis. These were consistent with the adverse events declared in the scientific literature for dapagliflozin. Regarding vital signs, no clinically significant fluctuations were observed in the blood pressure or radial pulse of the study subjects. In addition, no clinically significant fluctuations in the blood glucose levels measurement were recorded in any of the subjects.

Following oral administration of dapagliflozin, the C_{max} was attained within 2 hours under fasting state. For test formulation the mean value for C_{max} was 85.47 (ng/mL), while for the reference product was 81.65 (ng/mL). The concentration versus time profiles of dapagliflozin (10 mg, single-dose) were almost identical for test and reference product after administration to healthy human subjects under fasting conditions (see Figure 1).

The mean values calculated for the pharmacokinetic parameters were similar for the IMPs (see Table III). However, for the reference product inconsiderably lower values were obtained for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ in comparison with the test product. For test formulation, the mean AUC_{0-t} was 495.13 (hr*ng/mL) and mean $AUC_{0-\infty}$ was 498.92 (hr*ng/mL), while for the reference

Table I. Demographic characteristics of the subjects who completed the study

Characteristic		Value
Number of subjects		38
Gender (number)	- Women	12
	-Men	26
Age (years, mean ± SD*)		29.9 ± 7.61
Weight (kg, mean ± SD*)		71.83 ± 12.332
Height (cm, mean ± SD*)		173.14 ± 12.332
Smoker	- Yes	16
	- No	22

*SD – standard deviation

Table II. Adverse events recorded during and at the study of the bioequivalence clinical trial

During the study	At the end of the study
6 cases of increased triglycerides; 1 case of leukocyturia; 1 case of increased AST 1 case of increased total bilirubin;	1 case of positive nitrites in urine; 1 case of decreased platelets; 1 case of atrio-ventricular block 1st degree; 1 case of leukocytosis

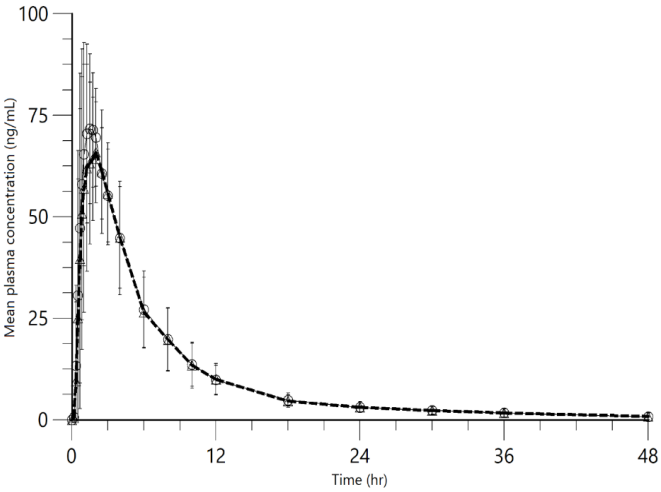

Fig. 1. Mean plasma concentration of dapagliflozin after administration of test product Dapagliflozin 10 mg immediate release tablets, developed by Sun Pharma, India (with full line) and the reference product Farxiga®, AstraZeneca, immediate release tablets (with dotted line), in 38 Caucasian subjects under fasting conditions

Table III. Main pharmacokinetic parameters of dapagliflozin in 38 Caucasian healthy subjects following administration of dapagliflozin 10 mg immediate release tablets under fasting conditions

Pharmacokinetic parameter	Mean		SD[1]		CV%[2]		Median	
	R	T	R	T	R	T	R	T
C_{max} (ng/mL)	81.65	85.47	26.32	25.57	32.24	29.92	77.32	76.97
AUC_{0-t} (hr*ng/mL)	480.92	495.13	122.50	123.50	25.47	24.94	449.60	468.44
$AUC_{0-\infty}$ (hr*ng/mL)	484.02	498.92	120.49	121.24	24.89	24.30	449.90	472.70
$t_{1/2}$ (hr)	16.60	14.04	10.03	5.64	60.45	40.19	14.79	14.14
t_{max} (hr)	1.80	1.64	0.71	0.73	39.45	44.65	1.75	1.50
k_{el} (hr^{-1})	0.05	0.06	0.02	0.03	46.72	40.19	0.05	0.05

SD1 – standard deviation; CV%2 – coefficient of variation; T represents Test Product (dapagliflozin 10 mg immediate release tablets developed by Sun Pharma, India); R represents Reference Product (Farxiga® 10 mg immediate release tablets, AstraZeneca)

Table IV. Bioequivalence evaluation of pharmacokinetic parameters of dapagliflozin after administration of 10 mg immediate release tablet (test and reference), in 38 healthy Caucasian subjects, under fasting conditions

Dependent	Units	CI 90 Lower	CI 90 Upper	Ratio %Ref	Bioequivalence conclusion
Ln(C_{max})	ng/mL	96.08	115.13	105.17	Bioequivalent
Ln(AUC_{0-t})	hr*ng/mL	101.02	105.31	103.14	Bioequivalent
Ln($AUC_{0-\infty}$)	hr*ng/mL	101.19	105.40	103.27	Bioequivalent

*CI – confidence interval (90%); Bioequivalent if 90% CI: 80.00-125.00%

product the mean results were slightly lower for both AUC_{0-t} (480.92 hr*ng/mL) and $AUC_{0-\infty}$ (484.02 hr*ng/mL), respectively.

On the other hand, for $t_{1/2}$ (hr) the mean value obtained was slightly higher for the reference product (16.60 hr) than for the test product (14.04 hr). Regarding the mean t_{max}, the value obtained for test product was 1.64 hours while for reference was 1.80 hours.

The results of the bioequivalence assessment under fasting state of subjects and the conclusion of bioequivalence for the evaluated PK parameters are summarized in Table IV.

The 90% confidence intervals for the ratio of test (T) and reference (R) product averages (least squares means) derived from the analysis of log (natural) transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were within 80.00-125.00% acceptance range. For C_{max} the ratios of least-squares means (with 90% confidence intervals) was 105.17% (96.08% – 115.13%). For AUC_{0-t} and $AUC_{0-\infty}$ the ratios of least-squares means (with 90% confidence intervals) were 103.14% (101.02% – 105.31%), 103.27% (101.19% - 105.40%), respectively.

Conclusions

Taking into consideration these results, the immediate release tablets newly developed by Sun Pharmaceutical Industries, India, containing Dapagliflozin 10 mg, were concluded to be bioequivalent with the reference product (Farxiga®, AstraZeneca Pharmaceuticals LP, USA) in healthy adult Caucasian subjects under fasting conditions.

Authors' contribution

MO (Data curation; Formal analysis; Writing – original draft)

AM (Conceptualization; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Writing – review & editing)

AM Gheldiu (Data curation; Formal analysis; Software; Writing – review & editing)

DIP (Data curation; Formal analysis; Software)

SB (Funding acquisition; Investigation; Project administration; Resources; Supervision)

AK (Funding acquisition; Investigation; Methodology; Supervision; Validation)

LV (Formal analysis; Investigation; Supervision; Validation; Visualization; Writing – review & editing)

Conflict of interest

None to declare.

References

1. European Medicines Agency, Committee for Medicinal Products for Human Use, Guideline on the investigation of bioequivalence. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-bioequivalence-rev1_en.pdf [accessed June 22nd 2019]
2. Pop DI, Oroian M, Bhardwaj S, Marcovici A, Khuroo A, Kochhar R, Vlase L. Bioequivalence of two formulations of gliclazide in a randomized crossover study in healthy Caucasian subjects under fed condition. Farmacia 2018; 66(4): 597-601.
3. U.S. Department of Health and Human Services Food and Drug Administration, Bioavailability and Bioequivalence Studies for Orally Administered Drug Products- General Considerations. http://academy.gmp-compliance.org/guidemgr/files/UCM154838.PDF [accessed June 22nd 2019]
4. Pop DI, Oroian M, Bhardwaj S, Marcovici A, Khuroo A, Kochhar R, Vlase L. Bioequivalence of two formulations of gliclazide in a randomized crossover study in healthy Caucasian subjects under fasting conditions. Clin Pharm Drug Dev 2019; 8(1): 16-21.
5. International Council for Harmonisation, Topic E8 General considerations for clinical trials. https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-8-general-considerations-clinical-trials-step-5_en.pdf [accessed June 22nd 2019]
6. Pop DI, Gheldiu AM, Oroian M, Marcovici A, Bhardwaj S, Khuroo A, Kochhar R, Vlase L. Effect of food on the pharmacokinetics of gliclazide 60 mg modified release tablet in healthy Caucasian volunteers. Acta Med Marisiensis 2018; 64(4): 161-168.
7. International Diabetes Federation, Diabetes Atlas, 8th edition 2017. https://diabetesatlas.org/IDF_Diabetes_Atlas_8e_interactive_EN/ [accessed June 22nd 2019]
8. International Diabetes Federation, Clinical Practice Recommendations for managing Type 2 Diabetes in Primary Care. https://www.idf.org/e-library/guidelines/128-idf-clinical-practice-recommendations-for-managing-type-2-diabetes-in-primary-care.html [accessed June 22nd 2019]
9. Kahn SE, Cooper ME, Del Prato S. Pathophysiology and treatment of type 2 diabetes: perspectives on the past, present and future. Lancet 2014; 383(9922): 1068–1083.
10. McGurnaghan SJ, Brierley L, Caparrotta TM et al. The effect of dapagliflozin on glycaemic control and other cardiovascular disease risk factors in type 2 diabetes mellitus: a real-world observational study. Diabetologia 2019; 62: 621-632.
11. Oroian M, Marcovici A, Pop DI, Bhardwaj S, Khuroo A, Gheldiu AM, Vlase L. Kinetics of dapagliflozin after single dose oral administration of a 10 mg immediate release tablet. Studia UBB Chemia 2019; LXIV(2, Tom I): 297-308.
12. List JF, Woo V, Morales E, Tang W, Fiedorek FT. Sodium-glucose cotransport inhibition with dapagliflozin in type 2 diabetes. Diabetes Care 2009; 32(4): 650–657.
13. Henry RR, Rosenstock J, Edelman S et al. Exploring the potential of the SGLT2 inhibitor dapagliflozin in type 1 diabetes: a randomized, double-blind, placebo-controlled pilot study. Diabetes Care 2015; 38(3): 412–419.
14. Ferrannini E, Jimenez Ramos S, Salsali A, Tang W, List JF. Dapagliflozin monotherapy in type 2 diabetic patients with inadequate glycemic control by diet and exercise. Diabetes Care 2010; 33(10): 2217–2224.
15. U.S. Department of Health and Human Services Food and Drug Administration, Draft Guidance on Dapagliflozin Propanediol. https://www.accessdata.fda.gov/drugsatfda_docs/psg/Dapagliflozin%20propanediol%20_oral%20tablet_202293_RC06-15.pdf [accessed June 22nd 2019]