PDL NEW DRUG REVIEW

Proprietary Name: Invokana®
Common Name: canagliflozin
PDL Category: Diabetic- Other

Comparable Products	Preferred Drug List Status
Januvia	Preferred with Conditions
Metformin	Preferred
Onglyza	Preferred with Conditions

Summary

Indications and Usage: Adjunct treatment to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (DM). It is not recommended for use in those with type 1 DM or for the treatment of diabetic ketoacidosis. This is a pregnancy category C medication. The safety and efficacy of use in children under the age of 18 have not been established.

Drug Interactions: When Invokana® 300mg was given concomitantly with digoxin, there was an increase in the area area-under-the-curve (AUC) and mean peak drug concentration of digoxin. Therefore, it is recommended that appropriate monitoring take place if this combination is used.

The concomitant use of canagliflozin with rifampin, a non-selective inducer of several UGT enzymes, decreased the AUC by 51%, which may decrease its efficacy. Therefore, it is recommended that if inducers of UGT enzymes (eg rifampin, phenytoin, phenobarbital, ritonavir) are given concomitantly with Invokana® that it be considered to increase the dose to 300mg in those taking 100mg QD who also have an estimated glomerular filtration rate (eGFR) of at least 60ml/min/1.73m^2 and require additional glycemic control. Additionally, consider other antihyperglycemic therapy in those with an eGFR of 45-60ml/min/1.73 m^2.

Dosage Forms: Capsule-shaped, film-coated Tablets: 100mg, 300mg.

Recommended Dosage: Take 100mg once daily, before the first meal of the day. In those who tolerate this dose, have an eGFR of at least 60ml/min/1.73m^2, and require additional glycemic control, the dose may be increased to 300mg once daily. Correcting volume depletion in those with this condition should be done prior to starting treatment with Invokana®.

Invokana® may increase the risk of hypoglycemia, and an even further risk may occur if it is used concomitantly with insulin or an insulin secretagogue. Therefore, a lower insulin or insulin secretagogue may be needed in those who use this combination.

Dosing adjustment is not required in those with mild renal impairment; however, the dose is limited to 100mg once daily in those with moderate renal impairment with an eGFR ranging from 45-60ml/min/1.73m^2. Invokana® should not be used in those with an eGFR that is less than 45ml/min/1.73m^2. Due to the dosing recommendations in those with renal impairment, it is recommended that renal assessment be performed prior to starting treatment with Invokana®.

Dosing adjustment is not required in those with mild or moderate hepatic impairment. Furthermore, as use in those with severe hepatic impairment has not been studied, use in this population is not recommended.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions = reported % incidence for drug minus reported % incidence for placebo.* The most common adverse events reported with Invokana® 100mg/300mg include female genital mycotic infections (includes vulvovaginal candidiasis, vulvovaginal mycotic infection, vulvovaginitis, vaginal

infection, vulvitis, and genital infection fungal; 7.2%/8.2%), urinary tract infections (includes urinary tract infection, cystitis, kidney infection, and urosepsis; 1.9%/0.3%), increased urination (includes polyuria, pollakiuria, urine output increased, micturition urgency, and nocturia; 4.5%/3.8%), male genital mycotic infections (includes balanitis or balanoposthitis, balanitis candida, and genital infection fungal; 3.6%/3.1%), vulvovaginal pruritus (1.6%/3%), thirst (2.6%/2.1%), constipation (0.9%/2.2%), and nausea (0.7%/0.8%).

Hyperkalemia may occur with Invokana® use. Additionally, those with moderate renal impairment who are taking medications that block potassium excretion, such as potassium-sparing diuretics, are more likely to develop hyperkalemia.

Contraindications: Hypersensitivity to canagliflozin or any component of the product; Severe renal impairment (eGFR <30ml/min/1.73 m^2), end stage renal disease (ESRD), or those on dialysis.

Manufacturer: Janssen Pharmaceuticals, Inc

Analysis: Canagliflozin, the active ingredient in Invokana® is an inhibitor of sodium-glucose co-transporter 2 (SGLT2). This transporter is in the renal proximal tubules, and is responsible for most of the reabsorption of filtered glucose from the tubular lumen. Canagliflozin inhibiting the SGLT2 results in reduced reabsorption of filtered glucose, as well as lowering the renal threshold for glucose (RT_G). Thus, urinary glucose excretion is increased.

Several randomized, double-blind, placebo- and active-controlled (the DPP-4 sitagliptin and the sulfonylurea glimepiride) studies were performed to assess the safety and efficacy of canagliflozin in adults with type 2 DM. Overall, clinical studies suggested that clinically and statistically significant improvements in HbA1c were seen with Invokana® as compared with placebo.

Specifically, the mean change from baseline in HbA1c levels in the monotherapy studies were -0.77% with the 100mg group and -1.03% with the 300mg group as compared with 0.14% with placebo. Additionally, 45% of the 100mg dose group achieved a goal of HbA1c <7% as compared with 62% of the 300mg dose group and 21% of the placebo group. In one of the combination trials, Invokana® plus metformin was compared with placebo plus metformin, and the mean change from baseline in HbA1c levels were -0.79% with the 100mg/metformin group and -0.94% with the 300mg/metformin group as compared with -0.17% with the placebo/metformin group. A second combination trial compared Invokana® plus metformin with glimepiride plus metformin, and resultant mean changes from baseline in HbA1c were -0.82% with the 100mg/metformin group and -0.93% with the 300mg/metformin group as compared with -0.81% with the glimepiride/metformin group. In a combination trial comparing Invokana® 300mg/metformin/sulfonylurea with sitagliptin 100mg/metformin/sulfonylurea, the mean change from baseline in HbA1c was -1.03% with the Invokana® group as compared with -0.66% with the sitagliptin group.

Furthermore, Invokana® has been approved for use as monotherapy, as well as in combination with metformin, sulfonylureas, metformin and sulfonylureas, thiazolidinediones (TZDs), and insulin.

There is no evidence at this time to support that Invokana® is more efficacious or safer than the currently available, more cost effective medications. Therefore, it is recommended that Invokana® remain non-preferred and be available to the few who are unable to tolerate any preferred medications.

PDL Placement:

- ☐ **Preferred**
- ☒ **Non-Preferred**
- ☐ **Preferred with Conditions**

References

[1] Invokana® [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc; 2013.