3 Sep 2022

Sitagliptin Hydrochloride Monohydrate

Film coated tablet

COMPOSITIONS :

Sitagliptin Hydrochloride Monohydrate Film coated tablet 50 mg, each film coated tablet contains : Sitagliptin hydrochloride monohydrate 56.687 mg equivalent with Sitagliptin 50 mg.

Sitagliptin Hydrochloride Monohydrate Film coated tablet 100 mg, each film coated tablet contains : Sitagliptin hydrochloride monohydrate 113.374 mg equivalent with Sitagliptin 100 mg.

PHARMACOLOGY :

***Mechanism of action* :**

Sitagliptin is a DPP-4 inhibitor, which is believed to exert its action in patients with type 2 diabetes by slowing the inactivation of incretin hormones. Concentrations of the active intact hormones are increased by Sitagliptin Hydrochloride Monohydrate, thereby increasing and prolonging the action of these hormones. Incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are released by the intestine throughout the day, and levels are increased in response to a meal. These hormones are rapidly inactivated by the enzyme, DPP-4. The incretins are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells by intracellular signaling pathways involving cyclic AMP. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, leading to reduced hepatic glucose production. By increasing and prolonging active incretin levels, Sitagliptin hydrochloride monohydrate increases insulin release and decreases glucagon levels in the circulation in a glucose-dependent manner. Sitagliptin demonstrates selectively for DPP-4 and does not inhibit DPP-8 or DPP-9 activity in vitro at concentrations approximating those from therapeutic doses.

Pharmacokinetic :

This study was conducted using open label, randomized, two-periods, two-treatment, crossover study in fasting conditions with 7 (seven) days washed-out period between each period.

The bioequivalence rate and extend of absorption were proven for both preparations by assessing geometric means as well as by statistic with a 90% Confidence Interval (CI) with $\alpha = 5.00\%$.

The main pharmacokinetic parameters of the test drug/reference drug, ratio were as follows : $AUC_{0\text{-}48h}$: 102.80 (100.16 - 105.49)% with CV Intra Subjects was 5.20% and C_{max} : 103.68 (94.16 - 114.15%) with CV Intra subjects was 19.42%.

Whilst T_{max} of the test drug/reference drug were respectively 3.00 (1.00 – 5.00) h and 2.50 (0.50 – 5.00) h; mean $T_{1/2}$ were respectively 7.00 ± 0.70 h and 7.02 ± 0.87 h; and mean Slope were respectively (-0.10) ± 0.01 h and (-0.10) ± 0.01 h.

Conclusion : Since the 90% Confidence Interval (CI) with $\alpha = 5.00\%$ for $AUC_{0\text{-}48h}$ and $AUC_{0\text{-}\infty}$ ratios as well as Cmax were within the range of 80.00 - 125.00% interval, it was concluded the

test drug **BIOEQUIVALENCE** in term of both rate and extent of absorption to the reference drug.

INDICATIONS :

- **Monotherapy**
  Sitagliptin Hydrochloride Monohydrate is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus.
- **Combination with Metformin or PPARγ agonist**
  Sitagliptin Hydrochloride Monohydrate is indicated in patients with type 2 diabetes mellitus to improve glycemic control in combination with Metformin or a PPARγ agonist (i.e. Thiazolidinediones) when the single agent alone, with diet and exercise, does not provide adequate glycemic control.
- **Combination with Metformin and Sulfonylurea**
  Sitagliptin Hydrochloride Monohydrate is indicated in patients with type 2 diabetes mellitus to improve glycemic control in combination with Metformin and a Sulfonylurea when dual therapy with these agent, with diet and exercise, does not provide adequate glycemic control.
- **Combination with Insulin**
  Sitagliptin Hydrochloride Monohydrate is also indicated as add-on to Insulin (with or without Metformin) when diet and exercise plus stable dose of Insulin do not provide adequate glycemic control.

When Sitagliptin Hydrochloride Monohydrate is used in combination with a Sulfonylurea or with Insulin, a lower dose of the Sulfonylurea or Insulin may be considered to reduce the risk of hypoglycemia.

CONTRAINDICATIONS :

None.

DOSAGE AND ADMINISTRATIONS :

Recommended dosing

The recommended dose of Sitagliptin Hydrochloride Monohydrate is 100 mg once daily as monotherapy or as combination therapy with Metformin or a PPARγ agonist (e.g., Thiazolidinediones), Metformin and Sulfonylurea, stable dose of Insulin (with or without Metformin). Sitagliptin Hydrochloride Monohydrate can be taken with or without food.

When used in combination with Metformin or a PPARγ agonist, the dose of Metformin or PPARγ agonist should be maintained, and Sitagliptin Hydrochloride Monohydrate administered concomitantly.

When Sitagliptin Hydrochloride Monohydrate is used in combination with a Sulfonylurea or with Insulin, a lower dose of the Sulfonylurea or Insulin may be considered to reduce the risk of hypoglycaemia.

Patients with renal impairment

Because there is a dosage adjustment based upon renal function, assessment of renal function is recommended prior to initiation of Sitagliptin Hydrochloride Monohydrate and periodically thereafter.

For patients with mild renal impairment (estimated glomerular filtration rate (eGFR ≥ 60 mL/min/1.73 m^2 to < 90 mL/min/1.73 m^2), no dosage adjustment for Sitagliptin Hydrochloride Monohydrate is required.

For patients with moderate renal impairment (eGFR ≥ 45 mL/min/1.73 m^2 to < 60 mL/min/1.73 m^2), no dosage adjustment for Sitagliptin Hydrochloride Monohydrate is required.

For patients with moderate renal impairment (eGFR ≥ 30 mL/min/1.73 m^2 to < 45 mL/min/1.73 m^2), the dose of Sitagliptin Hydrochloride Monohydrate is 50 mg once daily.

For patients with severe renal impairment (eGFR ≥ 15 mL/min/1.73 m^2 to < 30 mL/min/1.73 m^2) or with end-stage renal disease (ESRD) (eGFR < 15 mL/min/1.73 m^2), including those requiring hemodialysis or peritoneal dialysis, the dose of Sitagliptin Hydrochloride Monohydrate is 25 mg once daily. Sitagliptin Hydrochloride Monohydrate may be administered without regard to the timing of dialysis.

WARNINGS AND PRECAUTIONS :

Sitagliptin Hydrochloride Monohydrate should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Pancreatitis

There have been reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis (see **ADVERSE DRUG REACTIONS**), in patients taking **Sitagliptin Hydrochloride Monohydrate**. After initiation of **Sitagliptin Hydrochloride Monohydrate**, patients should be observed carefully for signs and symptoms of pancreatitis. Patients should be informed of the characteristic symptom of acute pancreatitis; persistent, severe abdominal pain. Resolution of pancreatitis has been observed after discontinuation of Sitagliptin. If pancreatitis is suspected, **Sitagliptin Hydrochloride Monohydrate** and other potentially suspect medicinal products, should be discontinued.

Use in patients with renal impairment

A dosage adjustment is recommended in patients with EGFR < 45 mL/min/1.73 m^2), as well as in ESRD patients requiring hemodialysis or peritoneal dialysis (see **DOSAGE AND ADMINISTRATIONS**).

Use with medications known to cause hypoglycemia

As is typical with other antihyperglycemic agents, hypoglycemia has been observed when **Sitagliptin Hydrochloride Monohydrate** was used in combination with Insulin or a Sulfonylurea. Therefore, a lower dose of Sulfonylurea or Insulin may be required to reduce the risk of hypoglycemia.

Macrovascular outcomes

There have been no establishing conclusive evidence of macrovascular risk reduction with **Sitagliptin Hydrochloride Monohydrate** or any other anti-diabetic drug.

Bullous pemphigoid

Cases of bullous pemphigoid requiring hospitalization have been reported with DPP-4 inhibitor use. In reported cases, patients typically recovered with topical or systemic immunosuppressive treatment and discontinuation of the DPP-4 inhibitor. Tell patients to report development of blisters or erosions while receiving **Sitagliptin Hydrochloride Monohydrate**. If bullous pemphigoid is suspected, **Sitagliptin Hydrochloride Monohydrate** should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

DRUG INTERACTIONS :

Digoxin

There was a slight increase in the area under the curve (AUC) and mean peak drug concentration (Cmax) of Digoxin with the co-administration of 100 mg Sitagliptin for 10 days. Patients receiving Digoxin should be monitored appropriately. No dosage adjustment of Digoxin of **Sitagliptin Hydrochloride Monohydrate** is recommended.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy category B : This drug should be used during pregnancy only if clearly needed.

Nursing mothers

Sitagliptin is secreted in the milk of lactating at a milk to plasma ratio of 4 : 1. It is not known whether Sitagliptin is excreted in human milk. Because many drug are excreted in human milk, caution should be exercised when **Sitagliptin Hydrochloride Monohydrate** is administered to a nursing woman.

Pediatric use

Safety and effectiveness of **Sitagliptin Hydrochloride Monohydrate** in pediatric patients have not been established.

Geriatric use

No overall differences in safety or effectiveness were observed between subjects 65 years and over and younger subjects. While this and other reported experience have not identified differences in responses between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out.

This drug is known to be substantially excreted by the kidney. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection in the elderly, and it may be useful to assess renal function in these patients prior to initiating dosing and periodically thereafter (**DOSAGE AND ADMINISTRATIONS**).

ADVERSE DRUG REACTIONS :

- Both monotherapy and combination therapy with Metformin, Pioglitazone, the overall incidence of adverse reactions, hypoglycemia, and discontinuation of therapy due to clinical adverse reactions with **Sitagliptin Hydrochloride Monohydrate** was also similar to placebo. In combination with Glimepiride, with or without Metformin, the overall incidence

of clinical adverse reactions with **Sitagliptin Hydrochloride Monohydrate** was higher than with placebo, in part related to a higher incidence of hypoglycemia; the incidence of discontinuation due to clinical adverse reactions was similar to placebo.

- Patients receiving **Sitagliptin Hydrochloride Monohydrate** as add-on therapy to stable-dose Insulin (with or without Metformin), there were no adverse reactions reported regardless of investigator assessment of causality in patients and more commonly than in patients given placebo, except for hypoglycemia. In patients receiving **Sitagliptin Hydrochloride Monohydrate** as add-on therapy while undergoing Insulin intensification (with or without Metformin), there were no drug-related adverse reactions reported that occurred with an incidence in patients treated with **Sitagliptin Hydrochloride Monohydrate** 100 mg and more commonly than in patients treated with placebo. In the two monotherapy, the add-on to Metformin and the add-on to Pioglitazone, the incidence of selected gastrointestinal adverse reactions in patients treated with **Sitagliptin Hydrochloride Monohydrate** was as follows : Abdominal pain, nausea, and diarrhea.
- Hypoglycemia
  When **Sitagliptin Hydrochloride Monohydrate** was co-administered with a Sulfonylurea or with Insulin, patients with at least one adverse reaction of hypoglycemia was higher than in the corresponding placebo.
- Post-marketing experience
  Additional adverse reactions have been identified during postapproval use of **Sitagliptin Hydrochloride Monohydrate** as monotherapy and/or in combination with other antihyperglycemic agents. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
  Hypersensitivity reactions including anaphylaxis, angioedema, rash, urticaria, cutaneous vasculitis, and exfoliative skin conditions including Stevens-Johnson syndrome (see **WARNINGS AND PRECAUTIONS**), hepatic enzyme elevations; acute pancreatitis, including fatal and non-fatal hemorrhagic and necrotizing pancreatitis (**WARNINGS AND PRECAUTIONS**), constipation, vomiting, headache, worsening renal function, including acute renal failure (sometimes requiring dialysis), bullous pemphigoid (see **WARNINGS AND PRECAUTIONS**, Bullous pemphigoid); arthralgia, myalgia, pain in extremity, back pain, pruritus.

OVERDOSAGE :

In healthy subjects, single doses of up to 800 mg **Sitagliptin Hydrochloride Monohydrate** were administered. Maximal mean increases in QTc of 8.0 msec were observed at a dose of 800 mg **Sitagliptin Hydrochloride Monohydrate**, a mean effect that is not considered clinically important. There is no experience with doses above 800 mg in humans.

In the event of an overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring

(including obtaining an electrocardiogram), and institute supportive therapy as dictated by the patient's clinical status.
Sitagliptin is modestly dialyzable. Prolonged hemodialysis may be considered if clinically appropriate. It is not known if Sitagliptin is dialyzable by peritoneal dialysis.

STORAGE :
Store below 30ºC. Keep out of reach of children.

PRESENTATIONS :
Sitagliptin Hydrochloride Monohydrate Film coated tablet 50 mg
Box, 2 blisters @ 14 film coated tablets
Reg. No. …

Sitagliptin Hydrochloride Monohydrate Film coated tablet 100 mg
Box, 2 blisters @ 14 film coated tablets
Reg. No. …

ON MEDICAL PRESCRIPTION ONLY

Manufactured by :
PT. AMAROX PHARMA GLOBAL
Bekasi – Indonesia