SUMMARY OF THE PRODUCT CHARACTERISTICS

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

TORSIT M 50+500
TORSIT M 50+1000

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TORSIT M 50+500
Each film-coated tablet contains:
Sitagliptin Phosphate Monohydrate USP Equivalent to Sitagliptin…….50 mg Metformin hydrochloride USP….500 mg
Colorant: Red oxide of Iron, Black oxide of Iron, Yellow oxide of Iron & Titanium dioxide

TORSIT M 50+1000
Each film-coated tablet contains:
Sitagliptin Phosphate Monohydrate USP Equivalent to Sitagliptin…….50 mg Metformin hydrochloride USP….1000 mg
Colorant: Red oxide of Iron, Black oxide of Iron & Titanium dioxide

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM:

Film-coated tablet

TORSIT M 50+500
Red, capsule shaped, film-coated tablets with "A20" debossed on one side and plain on the other side.

TORSIT M 50+1000
Red, capsule shaped, film-coated tablets with "A20" debossed on one side and plain on the other side

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications

Sitagliptin and metformin hydrochloride tablets are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both sitagliptin and metformin is appropriate.

4.2 Posology and method of administration Recommended Dosing

The dosage of sitagliptin and metformin hydrochloride tablets should be individualized on the basis of the patient's current regimen, effectiveness, and tolerability while not exceeding the maximum recommended daily dose of 100 mg sitagliptin and 2,000 mg metformin. Initial combination therapy or maintenance of combination therapy should be individualized and left to the discretion of the health care provider.

Sitagliptin and metformin hydrochloride tablets should generally be given twice daily with meals, with gradual dose escalation, to reduce the gastrointestinal (GI) side effects due to metformin. Sitagliptin and metformin hydrochloride tablets must not be split or divided before swallowing.
The starting dose of sitagliptin and metformin hydrochloride tablets should be based on the patient's current regimen. Sitagliptin and metformin hydrochloride tablets should be given twice daily with meals. The following doses are available:

50 mg sitagliptin/500 mg metformin hydrochloride

50 mg sitagliptin/1,000 mg metformin hydrochloride.

The recommended starting dose in patients not currently treated with metformin is 50 mg sitagliptin/500 mg metformin hydrochloride twice daily, with gradual dose escalation recommended to reduce gastrointestinal side effects associated with metformin.

The starting dose in patients already treated with metformin should provide sitagliptin dosed as 50 mg twice daily (100 mg total daily dose) and the dose of metformin already being taken. For patients taking metformin 850 mg twice daily, the recommended starting dose of sitagliptin and metformin hydrochloride tablets is 50 mg sitagliptin/1,000 mg metformin hydrochloride twice daily.

No studies have been performed specifically examining the safety and efficacy of sitagliptin and metformin hydrochloride tablets in patients previously treated with other oral antihyperglycemic agents and switched to sitagliptin and metformin hydrochloride tablets. Any change in therapy of type 2 diabetes should be undertaken with care and appropriate monitoring as changes in glycemic control can occur.

Recommendations for use in Renal Impairment

Assess renal function prior to initiation of sitagliptin and metformin hydrochloride tablets and periodically thereafter.

Sitagliptin and metformin hydrochloride tablets are contraindicated in patients with an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m2Sitagliptin and metformin hydrochloride tablets are not recommended in patients with an eGFR between 30 and less than 45 mL/min/1.73 m2 because these patients require a lower dosage of sitagliptin than what is available in the fixed combination sitagliptin and metformin hydrochloride tablets product.

Discontinuation for Iodinated Contrast Imaging Procedures

Discontinue sitagliptin and metformin hydrochloride tablets at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/min/1.73m^2; in patients with a history of liver disease, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart sitagliptin and metformin hydrochloride tablets if renal function is stable.

Pediatric Use

Safety and effectiveness of sitagliptin and metformin hydrochloride in pediatric patients under 18 years have not been established.

Geriatric Use

Sitagliptin and metformin hydrochloride tablets

Because sitagliptin and metformin are substantially excreted by the kidney, and because ageing can be associated with reduced renal function, renal function should be assessed more frequently in elderly patients.

Sitagliptin

Of the total number of subjects (N=3,884) in Phase II and III clinical studies of sitagliptin, 725 patients were 65 years and over, while 61 patients were 75 years and over. No overall differences in safety or effectiveness were observed between subjects 65 years and over and younger subjects. While this and other reported clinical experience have not identified differences in responses between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out.

Metformin hydrochloride

Controlled clinical studies of metformin did not include sufficient numbers of elderly patients

to determine whether they respond differently from younger patients, although other reported clinical experience has not identified differences in responses between the elderly and young patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy and the higher risk of lactic acidosis. Assess renal function more frequently in elderly patients.

Renal Impairment

Sitagliptin and metformin hydrochloride tablets

Sitagliptin and metformin hydrochloride tablets are not recommended in patients with an eGFR between 30 and less than 45 mL/min/1.73 m^2 because these patients require a lower dosage of sitagliptin than what is available in the fixed dose combination sitagliptin and metformin hydrochloride tablets product. Sitagliptin and metformin hydrochloride tablets are contraindicated in severe renal impairment, patients with an eGFR below 30 mL/min/1.73 m^2.

Sitagliptin

Sitagliptin is excreted by the kidney, and sitagliptin exposure is increased in patients with renal impairment. Lower dosages are recommended in patients with eGFR less than 45 mL/min/1.73 m^2 (moderate and severe renal impairment, as well as in ESRD patients requiring dialysis).

Metformin hydrochloride

Metformin is substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment.

Hepatic Impairment

Use of metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis. Sitagliptin and metformin hydrochloride are not recommended in patients with hepatic impairment.

4.3 Contraindications:

Sitagliptin and metformin hydrochloride tablets are contraindicated in patients with:

- Severe renal impairment (eGFR below 30 mL/min/1.73 m^2)
- Hypersensitivity to metformin hydrochloride.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insulin.
- History of a serious hypersensitivity reaction to sitagliptin and metformin hydrochloride tablets or sitagliptin (one of the components of sitagliptin and metformin hydrochloride tablets), such as anaphylaxis or angioedema.

4.4 Special warnings and precautions for

use Lactic Acidosis

Metformin hydrochloride

There have been post-marketing cases of metformin-associated lactic acidosis, including fatal cases. These cases had a subtle onset and were accompanied by nonspecific symptoms such as malaise, myalgias, abdominal pain, respiratory distress, or increased somnolence; however, hypothermia, hypotension and resistant bradyarrhythmias have occurred with severe acidosis. Metformin-associated lactic acidosis was characterized by elevated blood lactate concentrations (>5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), and an increased lactate/pyruvate ratio; metformin

plasma levels were generally >5 mcg/mL. Metformin decreases liver uptake of lactate increasing lactate blood levels which may increase the risk of lactic acidosis, especially in patients at risk.

If metformin-associated lactic acidosis is suspected, general supportive measures should be instituted promptly in a hospital setting, along with immediate discontinuation of sitagliptin and metformin hydrochloride tablets. In sitagliptin and metformin hydrochloride tablets-treated patients with a diagnosis or strong suspicion of lactic acidosis, prompt hemodialysis is recommended to correct the acidosis and remove accumulated metformin (metformin hydrochloride is dialyzable, with a clearance of up to 170 mL/min under good hemodynamic conditions). Hemodialysis has often resulted in reversal of symptoms and recovery.
Educate patients and their families about the symptoms of lactic acidosis and if these symptoms occur instruct them to discontinue sitagliptin and metformin hydrochloride tablets and report these symptoms to their health care provider.

For each of the known and possible risk factors for metformin-associated lactic acidosis, recommendations to reduce the risk of and manage metformin-associated lactic acidosis are provided below:

Renal Impairment
The post-marketing metformin-associated lactic acidosis cases primarily occurred in patients with significant renal impairment. The risk of metformin accumulation and metformin-associated lactic acidosis increases with the severity of renal impairment because metformin is substantially excreted by the kidney. Clinical recommendations based upon the patient's renal function include
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- Before initiating sitagliptin and metformin hydrochloride tablets, obtain an estimated glomerular filtration rate (eGFR).
- Sitagliptin and metformin hydrochloride tablets are contraindicated in patients with an eGFR below 30 mL/min/1.73 m2
- Sitagliptin and metformin hydrochloride tablets are not recommended in patients with an eGFR between 30 and less than 45 mL/min/1.73 m2 because these patients require a lower dosage of sitagliptin than what is available in the fixed combination sitagliptin and metformin hydrochloride tablets product.
- Obtain an eGFR at least annually in all patients taking sitagliptin and metformin hydrochloride tablets. In patients at increased risk for the development of renal impairment (e.g., the elderly), renal function should be assessed more frequently.

Drug Interactions
The concomitant use of sitagliptin and metformin hydrochloride with specific drugs may increase the risk of metformin-associated lactic acidosis: those that impair renal function, result in significant hemodynamic change, interfere with acid-base balance or increase metformin accumulation. Therefore, consider more frequent monitoring of patients.

Age 65 or Greater
The risk of metformin-associated lactic acidosis increases with the patient's age because elderly patients have a greater likelihood of having hepatic, renal, or cardiac impairment than younger patients. Assess renal function more frequently in elderly patients.

Radiological Studies with Contrast
Administration of intravascular iodinated contrast agents in metformin-treated patients has led to an acute decrease in renal function and the occurrence of lactic acidosis. Stop

sitagliptin and metformin hydrochloride tablets at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/min/1.73 m2; in patients with a history of hepatic impairment, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure, and restart sitagliptin and metformin hydrochloride tablets if renal function is stable.

Surgery and Other Procedures
Withholding of food and fluids during surgical or other procedures may increase the risk for volume depletion, hypotension and renal impairment. Sitagliptin and metformin hydrochloride tablets should be temporarily discontinued while patients have restricted food and fluid intake.

Hypoxic States
Several of the postmarketing cases of metformin-associated lactic acidosis occurred in the setting of acute congestive heart failure (particularly when accompanied by hypoperfusion and hypoxemia). Cardiovascular collapse (shock), acute myocardial infarction, sepsis, and other conditions associated with hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur, discontinue sitagliptin and metformin hydrochloride tablets.

Excessive Alcohol Intake
Alcohol potentiates the effect of metformin on lactate metabolism and this may increase the risk of metformin-associated lactic acidosis. Warn patients against excessive alcohol intake while receiving sitagliptin and metformin hydrochloride tablets.

Hepatic Impairment
Patients with hepatic impairment have developed with cases of metformin-associated lactic acidosis. This may be due to impaired lactate clearance resulting in higher lactate blood levels. Therefore, avoid use of sitagliptin and metformin hydrochloride tablets in patients with clinical or laboratory evidence of hepatic disease.

Pancreatitis
There have been postmarketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, in patients taking sitagliptin and metformin hydrochloride. After initiation of sitagliptin and metformin hydrochloride, patients should be observed carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, sitagliptin and metformin hydrochloride should promptly be discontinued and appropriate management should be initiated. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using sitagliptin and metformin hydrochloride.

Heart Failure
An association between dipeptidyl peptidase-4 (DPP-4) inhibitor treatment and heart failure has been observed in cardiovascular outcomes trials for two other members of the DPP-4 inhibitor class. These trials evaluated patients with type 2 diabetes mellitus and atherosclerotic cardiovascular disease.

Consider the risks and benefits of sitagliptin and metformin hydrochloride prior to initiating treatment in patients at risk for heart failure, such as those with a prior history of heart failure and a history of renal impairment, and observe these patients for signs and symptoms of heart failure during therapy. Advise patients of the characteristic symptoms of heart failure and to immediately report such symptoms. If heart failure develops, evaluate and manage according to current standards of care and consider discontinuation

of sitagliptin and metformin hydrochloride.

Assessment of Renal Function
Metformin and sitagliptin are known to be substantially excreted by the kidney.

Metformin hydrochloride
Sitagliptin and metformin hydrochloride tablets are contraindicated in patients with severe renal impairment.

Sitagliptin
There have been postmarketing reports of worsening renal function, including acute renal failure, sometimes requiring dialysis. Before initiation of therapy with sitagliptin and metformin hydrochloride and at least annually thereafter, renal function should be assessed. In patients in whom development of renal dysfunction is anticipated, particularly in elderly patients, renal function should be assessed more frequently and sitagliptin and metformin hydrochloride discontinued if evidence of renal impairment is present.

Vitamin B12 Levels
In controlled clinical trials of metformin of 29 weeks duration, a decrease to subnormal levels of previously normal serum Vitamin B12 levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B12 absorption from the B12-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or Vitamin B12 supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on sitagliptin and metformin hydrochloride and any apparent abnormalities should be appropriately investigated and managed.

Certain individuals (those with inadequate Vitamin B12 or calcium intake or absorption) appear to be predisposed to developing subnormal Vitamin B12 levels. In these patients, routine serum Vitamin B12 measurements at two-to three-year intervals may be useful.

Change in Clinical Status of Patients with Previously Controlled Type 2 Diabetes
A patient with type 2 diabetes previously well controlled on sitagliptin and metformin hydrochloride who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate, and metformin levels. If acidosis of either form occurs, sitagliptin and metformin hydrochloride must be stopped immediately and other appropriate corrective measures initiated.

Use with Medications Known to Cause Hypoglycemia Sitagliptin
When sitagliptin was used in combination with a sulfonylurea or with insulin, medications known to cause hypoglycemia, the incidence of hypoglycemia was increased over that of placebo used in combination with a sulfonylurea or with insulin. Therefore, patients also receiving an insulin secretagogue (e.g., sulfonylurea) or insulin may require a lower dose of the insulin secretagogue or insulin to reduce the risk of hypoglycemia.

Metformin hydrochloride
Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use but could occur when caloric intake is deficient when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as sulfonylureas and insulin) or ethanol. Elderly, debilitated, or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia

may be difficult to recognize in the elderly, and in people who are taking β-adrenergic blocking drugs.

Loss of Control of Blood Glucose
When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of glycemic control may occur. At such times, it may be necessary to withhold sitagliptin and metformin hydrochloride and temporarily administer insulin. Sitagliptin and metformin hydrochloride may be reinstituted after the acute episode is resolved.

Hypersensitivity Reactions
There have been post-marketing reports of serious hypersensitivity reactions in patients treated with sitagliptin, one of the components of sitagliptin and metformin hydrochloride tablets. These reactions include anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. Onset of these reactions occurred within the first 3 months after initiation of treatment with sitagliptin, with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, discontinue sitagliptin and metformin hydrochloride, assess for other potential causes for the event, and institute alternative treatment for diabetes.

Angioedema has also been reported with other DPP-4 inhibitors. Use caution in a patient with a history of angioedema with another DPP-4 inhibitor because it is unknown whether such patients will be predisposed to angioedema with sitagliptin and metformin hydrochloride.

Severe and Disabling Arthralgia
There have been post-marketing reports of severe and disabling arthralgia in patients taking DPP- 4 inhibitors. The time to onset of symptoms following initiation of drug therapy varied from one day to years. Patients experienced relief of symptoms upon discontinuation of the medication. A subset of patients experienced a recurrence of symptoms when restarting the same drug or a different DPP-4 inhibitor. Consider DPP-4 inhibitors as a possible cause for severe joint pain and discontinue drug if appropriate.

Bullous Pemphigoid
Post-marketing 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 and metformin hydrochloride tablets. If bullous pemphigoid is suspected, sitagliptin and metformin hydrochloride tablets should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

Macrovascular Outcomes
There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with sitagliptin and metformin hydrochloride.

Excipients
This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interactions with other medicinal products and other forms of interaction

Pharmacodynamic interactions

Carbonic Anhydrase Inhibitors

Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently cause a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs with sitagliptin and metformin hydrochloride may increase the risk of lactic acidosis. Consider more frequent monitoring of these patients.

Drugs that Reduce Metformin Clearance

Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter-2 [OCT2] / multidrug and toxin extrusion [MATE] inhibitors such as ranolazine, vandetanib, dolutegravir, and cimetidine) could increase systemic exposure to metformin and may increase the risk for lactic acidosis. Consider the benefits and risks of concomitant use.

Alcohol

Alcohol is known to potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake while receiving sitagliptin and metformin hydrochloride.

Insulin Secretagogues or Insulin

Coadministration of sitagliptin and metformin hydrochloride with an insulin secretagogue (e.g., sulfonylurea) or insulin may require lower doses of the insulin secretagogue or insulin to reduce the risk of hypoglycemia.

Use of Metformin with Other Drugs

Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving sitagliptin and metformin hydrochloride the patient should be closely observed to maintain adequate glycemic control.

Digoxin

There was a slight increase in the area under the curve (AUC, 11%) and mean peak drug concentration (Cmax, 18%) of digoxin with the coadministration of 100 mg sitagliptin for 10 days. Patients receiving digoxin should be monitored appropriately. No dosage adjustment of digoxin or sitagliptin and metformin hydrochloride is recommended.

4.6 Pregnancy and lactation Risk Summary

The limited available data with sitagliptin and metformin hydrochloride in pregnant women are not sufficient to inform a drug-associated risk for major birth defects and miscarriage. Published studies with metformin use during pregnancy have not reported a clear association with metformin and major birth defect or miscarriage risk.There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, preeclampsia, spontaneous abortions, preterm delivery, stillbirth, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, still

birth, and macrosomia related morbidity.

Data
Human Data
Published data from post-marketing studies do not report a clear association with metformin and major birth defects, miscarriage, or adverse maternal or fetal outcomes when metformin is used during pregnancy. However, these studies cannot definitely establish the absence of any risk because of methodological limitations, including small sample size and inconsistent comparator groups.

Lactation
Risk Summary
Sitagliptin and metformin hydrochloride tablets
There is no information regarding the presence of sitagliptin and metformin hydrochloride in human milk, the effects on the breastfed infant, or the effects on milk production. Limited published studies report that metformin is present in human milk. There are no reports of adverse effects on breastfed infants exposed to metformin. There is no information on the effects of metformin on milk production. Sitagliptin is present in rat milk and therefore possibly present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for sitagliptin and metformin hydrochloride and any potential adverse effects on the breastfed infant from sitagliptin and metformin hydrochloride or from the underlying maternal condition.

Females and Males of Reproductive Potential
Discuss the potential for unintended pregnancy with premenopausal women as therapy with metformin may result in ovulation in some anovulatory women.

4.7 Effects on ability to drive and use machines

Sitagliptin and metformin has no or negligible influence on the ability to drive and use machines. However, when driving or using machines, it should be taken into account that dizziness and somnolence have been reported with sitagliptin.

In addition, patients should be alerted to the risk of hypoglycaemia when Sitagliptin and metformin is used in combination with a sulphonylurea or with insulin.

4.8 UNDESIRABLE EFFECTS

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Sitagliptin and Metformin Coadministration in Patients with Type 2 Diabetes Inadequately Controlled on Diet and Exercise

The most common (≥5% of patients) adverse reactions reported in a 24-week placebo-controlled factorial study in which sitagliptin and metformin were coadministered to patients with type 2 diabetes inadequately controlled on diet and exercise are Diarrhea, Upper Respiratory Tract Infection and Headache.

Sitagliptin Add-on Therapy in Patients with Type 2 Diabetes Inadequately

Controlled on Metformin Alone
In a 24-week placebo-controlled trial of sitagliptin 100 mg administered once daily added to a twice daily metformin regimen, there were no adverse reactions reported regardless of investigator assessment of causality in ≥5% of patients and more commonly than in patients given placebo.

Gastrointestinal Adverse Reactions
The incidences of pre-selected gastrointestinal adverse experiences in patients treated with sitagliptin and metformin were similar to those reported for patients treated with metformin alone.

Sitagliptin in Combination with Metformin and Glimepiride
In a 24-week placebo-controlled study of sitagliptin 100 mg as add-on therapy in patients with type 2 diabetes inadequately controlled on metformin and glimepiride (sitagliptin, N=116; placebo, N=113), the adverse reactions reported regardless of investigator assessment of causality in ≥5% of patients treated with sitagliptin and more commonly than in patients treated with placebo were: hypoglycemia and headache.

Sitagliptin in Combination with Metformin and Rosiglitazone
The adverse reactions reported regardless of investigator assessment of causality in ≥5% of patients treated with sitagliptin and more commonly than in patients treated with placebo were: upper respiratory tract infection (sitagliptin, 15.5%; placebo, 6.2%), nasopharyngitis (11.0%, 9.3%), peripheral oedema (8.3%, 5.2%), and headache (5.5%, 4.1%).

Sitagliptin in Combination with Metformin and Insulin
The only adverse reaction reported regardless of investigator assessment of causality in ≥5% of patients treated with sitagliptin and more commonly than in patients treated with placebo was hypoglycemia

Hypoglycemia
When the combination of sitagliptin and metformin was coadministered with a sulfonylurea or with insulin, the percentage of patients reporting at least one adverse reaction of hypoglycemia was higher than that observed with placebo and metformin coadministered with a sulfonylurea or with insulin

Vital Signs and Electrocardiograms
With the combination of sitagliptin and metformin, no clinically meaningful changes in vital signs or in ECG (including in QTc interval) were observed.

Pancreatitis
The most common adverse experience in sitagliptin monotherapy reported regardless of investigator assessment of causality in ≥5% of patients and more commonly than in patients given placebo was nasopharyngitis.

Metformin hydrochloride
The most common (>5%) established adverse reactions due to initiation of metformin therapy are diarrhea, nausea/vomiting, flatulence, abdominal discomfort, indigestion, asthenia, and headache.

Laboratory Tests Sitagliptin
A small increase in white blood cell count (approximately 200 cells/microL difference in WBC vs placebo; mean baseline WBC approximately 6,600 cells/microL) was observed due to a small increase in neutrophils. This change in laboratory parameters is not considered to be

clinically relevant.

Metformin hydrochloride
In controlled clinical trials of metformin of 29 weeks duration, a decrease to subnormal levels of previously normal serum Vitamin B12 levels, without clinical manifestations, was observed in approximately 7% of patients.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Health care providers are asked to report any suspected adverse reactions to the marketing authorization holder, or, if available, via the national reporting system (see details below);

Paper based reporting: TMDA yellow card
Online reporting: https://sqrt.tmda.go.tz/
*USSD reporting: send a simple short text message to report any suspected Adverse Drug Reaction by dialing *152*00# and follow the instructions*

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Blood Glucose Lowering drugs, ATC code: A10BD07

Mechanism of action
Sitagliptin and metformin hydrochloride tablets

Sitagliptin and metformin hydrochloride tablets combine two antihyperglycemic agents with complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes mellitus: sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, and metformin hydrochloride, a member of the biguanide class.

Sitagliptin
Sitagliptin is a DPP-4 inhibitor, which is believed to exert its actions in patients with type 2 diabetes by slowing the inactivation of incretin hormones. Concentrations of the active intact hormones are increased by sitagliptin, 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 increases insulin release and decreases glucagon levels in the circulation in a glucose-dependent manner. Sitagliptin demonstrates selectivity for DPP-4 and does not inhibit DPP-8 or DPP-9 activity in vitro at concentrations approximating those from therapeutic doses.

Metformin hydrochloride
Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes mellitus, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral

antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Metformin does not produce hypoglycemia in either patients with type 2 diabetes mellitus or normal subjects (except in special circumstances and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

Pharmacodynamic effects Sitagliptin

In patients with type 2 diabetes mellitus, administration of sitagliptin led to inhibition of DPP-4 enzyme activity for a 24-hour period. After an oral glucose load or a meal, this DPP-4 inhibition resulted in a 2-to 3-fold increase in circulating levels of active GLP-1 and GIP, decreased glucagon concentrations, and increased responsiveness of insulin release to glucose, resulting in higher C-peptide and insulin concentrations. The rise in insulin with the decrease in glucagon was associated with lower fasting glucose concentrations and reduced glucose excursion following an oral glucose load or a meal. In studies with healthy subjects, sitagliptin did not lower blood glucose or cause hypoglycemia.

Sitagliptin and Metformin hydrochloride Coadministration

In a two-day study in healthy subjects, sitagliptin alone increased active GLP-1 concentrations, whereas metformin alone increased active and total GLP-1 concentrations to similar extents. Coadministration of sitagliptin and metformin had an additive effect on active GLP-1 concentrations. Sitagliptin, but not metformin, increased active GIP concentrations. It is unclear what these findings mean for changes in glycemic control in patients with type 2 diabetes mellitus.

Cardiac Electrophysiology

In a randomized, placebo-controlled crossover study, 79 healthy subjects were administered a single oral dose of sitagliptin 100 mg, sitagliptin 800 mg (8 times the recommended dose), and placebo. At the recommended dose of 100 mg, there was no effect on the QTc interval obtained at the peak plasma concentration, or at any other time during the study. Following the 800-mg dose, the maximum increase in the placebo-corrected mean change in QTc from baseline at 3 hours postdose was 8.0 msec. This increase is not considered to be clinically significant. At the 800-mg dose, peak sitagliptin plasma concentrations were approximately 11 times higher than the peak concentrations following a 100-mg dose.

In patients with type 2 diabetes mellitus administered sitagliptin 100 mg (N=81) or sitagliptin 200 mg (N=63) daily, there were no meaningful changes in QTc interval based on ECG data obtained at the time of expected peak plasma concentration.

5.2 Pharmacokinetic

properties Sitagliptin

The pharmacokinetics of sitagliptin have been extensively characterized in healthy subjects and patients with type 2 diabetes mellitus. Following a single oral 100-mg dose to healthy volunteers, mean plasma AUC of sitagliptin was 8.52 μM•hr, Cmax was 950 nM, and apparent terminal half- life (t1/2) was 12.4 hours. Plasma AUC of sitagliptin increased in a dose-proportional manner and increased approximately 14% following 100 mg doses at steady-state compared to the first dose. The intra-subject and inter-subject coefficients of variation for sitagliptin AUC were small (5.8% and 15.1%). The pharmacokinetics of sitagliptin was generally similar in healthy subjects and in patients with type 2 diabetes mellitus.

Absorption
Sitagliptin
After oral administration of a 100 mg dose to healthy subjects, sitagliptin was rapidly absorbed with peak plasma concentrations (median Tmax) occurring 1 to 4 hours postdose. The absolute bioavailability of sitagliptin is approximately 87%.

Effect of Food
Coadministration of a high-fat meal with sitagliptin had no effect on the pharmacokinetics of sitagliptin.

Metformin hydrochloride
The absolute bioavailability of a metformin hydrochloride 500-mg tablet given under fasting conditions is approximately 50 to 60%. Studies using single oral doses of metformin hydrochloride tablets 500 mg to 1,500 mg, and 850 mg to 2,550 mg (approximately 1.3 times the maximum recommended daily dosage), indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination.

Effect of Food
Food decreases the extent of and slightly delays the absorption of metformin, as shown by approximately a 40% lower mean peak plasma concentration (Cmax), a 25% lower area under the plasma concentration versus time curve (AUC), and a 35-minute prolongation of time to peak plasma concentration (Tmax) following administration of a single 850-mg tablet of metformin with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

Distribution

Sitagliptin
The mean volume of distribution at steady state following a single 100-mg intravenous dose of sitagliptin to healthy subjects is approximately 198 liters. The fraction of sitagliptin reversibly bound to plasma proteins is low (38%).

Metformin hydrochloride
The apparent volume of distribution (V/F) of metformin following single oral doses of metformin hydrochloride tablets 850 mg averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90% protein bound. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of metformin hydrochloride tablets, steady-state plasma concentrations of metformin are reached within 24 to 48 hours and are generally <1 mcg/mL. During controlled clinical trials of metformin, maximum metformin plasma levels did not exceed 5 mcg/mL, even at maximum doses.

Elimination

Sitagliptin
Approximately 79% of sitagliptin is excreted unchanged in the urine with metabolism being a minor pathway of elimination. The apparent terminal t1/2 following a 100 mg oral dose of sitagliptin was approximately 12.4 hours and renal clearance was approximately 350 mL/min.

Metformin hydrochloride
Following oral administration, approximately 90% of the absorbed drug is eliminated via

the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Metabolism

Sitagliptin

Following a [14C] sitagliptin oral dose, approximately 16% of the radioactivity was excreted as metabolites of sitagliptin. Six metabolites were detected at trace levels and are not expected to contribute to the plasma DPP-4 inhibitory activity of sitagliptin. In vitro studies indicated that the primary enzyme responsible for the limited metabolism of sitagliptin was CYP3A4, with contribution from CYP2C8.

Metformin hydrochloride

Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion.

Excretion

Sitagliptin

Following administration of an oral [14C] sitagliptin dose to healthy subjects, approximately 100% of the administered radioactivity was eliminated in faeces (13%) or urine (87%) within one week of dosing.

Elimination of sitagliptin occurs primarily via renal excretion and involves active tubular secretion. Sitagliptin is a substrate for human organic anion transporter-3 (hOAT-3), which may be involved in the renal elimination of sitagliptin. The clinical relevance of hOAT-3 in sitagliptin transport has not been established. Sitagliptin is also a substrate of p-glycoprotein (P-gp), which may also be involved in mediating the renal elimination of sitagliptin. However, cyclosporine, a P-gp inhibitor, did not reduce the renal clearance of sitagliptin.

Metformin hydrochloride

Elimination of metformin occurs primarily via renal excretion. Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination.

Specific Populations

Patients with Renal Impairment

Sitagliptin and metformin hydrochloride tablets

Studies characterizing the pharmacokinetics of sitagliptin and metformin after administration of sitagliptin and metformin hydrochloride tablets in renally impaired patients have not been performed.

Sitagliptin

An approximately 2-fold increase in the plasma AUC of sitagliptin was observed in patients with moderate renal impairment with eGFR of 30 to less than 45 mL/min/1.73 m^2, and an approximately 4-fold increase was observed in patients with severe renal impairment including patients with end-stage renal disease (ESRD) on hemodialysis, as compared to normal healthy control subjects.

Metformin hydrochloride

In patients with decreased renal function, the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased.

Patients with Hepatic Impairment

Sitagliptin and metformin hydrochloride tablets

Studies characterizing the pharmacokinetics of sitagliptin and metformin after administration of sitagliptin and metformin hydrochloride tablets in patients with hepatic impairment have not been performed.

Sitagliptin

In patients with moderate hepatic impairment (Child-Pugh score 7 to 9), mean AUC and Cmax of sitagliptin increased approximately 21% and 13%, respectively, compared to healthy matched controls following administration of a single 100-mg dose of sitagliptin. These differences are not considered to be clinically meaningful. There is no clinical experience in patients with severe hepatic impairment (Child-Pugh score >9).

Metformin hydrochloride

No pharmacokinetic studies of metformin have been conducted in patients with hepatic impairment.

Effects of Age, Body Mass Index (BMI), Gender, and Race

Sitagliptin

Based on a population pharmacokinetic analysis or a composite analysis of available pharmacokinetic data, BMI, gender, and race do not have a clinically meaningful effect on the pharmacokinetics of sitagliptin. When the effects of age on renal function are taken into account, age alone did not have a clinically meaningful impact on the pharmacokinetics of sitagliptin based on a population pharmacokinetic analysis. Elderly subjects (65 to 80 years) had approximately 19% higher plasma concentrations of sitagliptin compared to younger subjects.

Metformin hydrochloride

Limited data from controlled pharmacokinetic studies of metformin in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and Cmax is increased, compared to healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function.

Metformin pharmacokinetic parameters did not differ significantly between normal subjects and patients with type 2 diabetes mellitus when analyzed according to gender. Similarly, in controlled clinical studies in patients with type 2 diabetes mellitus, the antihyperglycemic effect of metformin was comparable in males and females.
No studies of metformin pharmacokinetic parameters according to race have been performed. In controlled clinical studies of metformin in patients with type 2 diabetes mellitus, the antihyperglycemic effect was comparable in Whites (n=249), Blacks (n=51), and Hispanics (n=24).

Pediatric Patients

Sitagliptin

Studies characterizing the pharmacokinetics of sitagliptin in pediatric patients have not been performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Crospovidone XL,
Microcrystalline cellulose (Avicel PH102),
Microcrystalline cellulose (Ceolus KG 1,000),
Povidone,
Sodium lauryl sulphate,
Sodium stearyl fumarate
Sorbitol
Opadry II Pink 85F540165 (For 50+500 mg strength)
Opadry II Brown 85F565107 (For 50+1000 mg strength)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30˚C.

6.5 Nature and contents of container

Sitagliptin and Metformin hydrochloride tablets 50 mg+ 500 mg and 50 mg+1000 mg are packed in Alu–Alu blisters of 10 tablets.

Proposed pack size: 1x10, 3x10, 10x10 tablets.
Not all pack sizes may be marketed.

7 Marketing Authorization Holder

Torrent Pharmaceuticals Ltd.,
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8. DATE OF PUBLICATION

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