To be sold by retail only under the prescription of Endocrinologists or Internal Medicine Specialists only.

IMEXTOR SR

1. **Generic Name**

   Imeglimin Hydrochloride Sustained Release Tablets 500 mg/1000 mg.

2. **Qualitative and quantitative composition**

   IMEXTOR SR 500/1000

   Each film coated tablet contains:

   Imeglimin Hydrochloride

   (As Sustained Release)……..….500 mg/1000 mg

   Excipients…….q.s.

   Color: Titanium Dioxide I.P.

   The Excipients used are Microcrystalline Cellulose, Povidone, Colloidal Silicon dioxide, Hydroxypropylmethyl Cellulose, Microcrystalline Cellulose, Colloidal Silicon dioxide, Magnesium Sterate, Instacoat universal white.

3. **Dosage form and strength**

   Dosage form: Film coated Sustained release tablet

   Strength: 500 mg and 1000 mg

4. **Clinical particulars**

4.1. Therapeutic indication

It is indicated for the treatment of type 2 diabetes mellitus inadequately controlled with diet and exercise alone.

4.2. Posology and method of administration

Posology

Take Imeglimin SR orally once daily with a post-meal. Patients taking two Imeglimin SR tablets should take the tablets together.

Individualize the dosage of Imeglimin SR on the basis of the patient's current regimen, effectiveness, and tolerability.

The maximum recommended dose of Imeglimin is 2000 mg per day.

For patients taking Imeglimin HCL immediate release 500 mg twice daily, the recommended equivalent dose of Imeglimin SR is one tablet of 1000 mg once daily.

For patients taking imeglimin HCL immediate release 1000 mg twice daily, the recommended equivalent dose of Imeglimin SR is two tablets of 1000 mg, once daily taken together.

If you miss a dose of Imeglimin Tablets, take it as soon as possible. However, if it is almost time for your next dose, skip the missed dose and go back to your regular schedule. Do not double the

dose.

Method of administration

Oral, Do not chew or crush the tablet. Swallow as whole.

4.3. Contraindications

- Patients with a history of hypersensitivity to the ingredients of this drug
- Patients with severe ketosis, diabetic coma or precoma, type 1 diabetes [Infusion, prompt correction of hyperglycemia with insulin is essential.]
- Patients with severe infections, before and after surgery, and with serious trauma

  [Because glycemic control by insulin injection is desired, administration of this drug is not suitable.]

4.4. Special warnings and precautions for use

The application of this drug should be considered only when the effect is insufficient after sufficient diet and exercise therapy, which are the basics of diabetes treatment.

In patients with renal dysfunction, excretion from the kidney is delayed depending on the degree of renal dysfunction, and the blood concentration of this drug increases. Patients with renal dysfunction, it is recommended to perform renal function check regularly, as the excretion of this drug may be delayed and the blood concentration of this drug may increase.

Before using this drug, patients should be fully informed of hypoglycemic symptoms and how to deal with them.

Since hypoglycemic symptoms may occur, care should be taken when administering to patients engaged in work at heights, driving a car, etc.

When administering, monitor blood glucose regularly to confirm the effect of the drug, and consider changing to a more appropriate treatment if the effect is insufficient after 3 months of administration.

The mechanism of action of this drug and may be partly in common with biguanide drugs, in addition, because co-administration of both drugs may increase gastrointestinal symptoms were observed compared to co-therapy with other antidiabetic drugs, care should be taken when selecting concomitant drugs.

Hypoglycemia may occur. In particular, hypoglycemia may occur when used concomitantly with insulin preparations, sulfonylureas, or rapid-acting insulin secretagogues. If hypoglycemic symptoms (initial symptoms: weakness, severe hunger, sweating, etc.) are observed, take appropriate measures such as ingesting food containing carbohydrates. However, if hypoglycemic symptoms are observed due to concomitant use with a α-glucosidase inhibitor, glucose should be administered.

It has been reported that biguanide drugs cause rare and serious lactic acidosis, and risk factors include renal dysfunction, liver dysfunction, conditions that are likely to accompany hypoxia, and dehydration (including concomitant use of drugs with diuretic effects), excessive alcohol intake, infectious diseases, the elderly, etc. are known.

In non-clinical studies using rats, no clear effects of this drug on blood lactate levels were observed,

and in clinical studies, the development of lactic acidosis was not observed. The mechanism of action of this drug may be partially in common with biguanide drugs.

People with renal dysfunction

The pharmacokinetics of this drug after a single oral administration in subjects with different degrees of renal dysfunction (classified based on eGFR measurements) were shown in subjects with normal renal function (eGFR 90 mL/ min/ 1.73 m2 or more). The results of a comparative study with the single oral administration of 1000 mg of the drug were as follows

Renal function (eGFR (mL/ min/ 1.73m^2))	Dosage (mg)	Number of examples	C_{max}	$AUC_{0\text{-last}}$
			Geometric mean ratio [90% confidence interval]	Geometric mean [90% confidence interval]
Mild (60 ≤ eGFR <90)	1000	6	1.42 [1.05, 1.91]	1.49 [1.03, 2.17]
Moderate (30 ≤ eGFR <60)	1000	6	1.52 [1.13, 2.05]	1.81 [1.25, 2.63]
Severe (15 ≤ eGFR <30)	500	6	1.50 [1.11, 2.02]	2.49 [1.71, 3.61]

Subjects with different degrees of renal dysfunction (classified based on measured values of CLcr (creatinine clearance) 500 mg once of this drug

Pharmacokinetics after repeated oral administration twice daily, subjects with normal renal function The results of a comparative study of (CLcr over 80 mL / min) with 500 mg of this drug once daily orally twice daily were as follows (data from foreigners).

Renal function (CL_{cr}*1)	Number of examples	C_{max}	AUC_{τ}
		Geometric mean ratio [90% confidence interval]	Geometric mean ratio [90% confidence interval]
Mild (50 ≤ CL_{cr} ≤ 80)	Four	1.28 [1.03, 1.59]	1.50 [1.16, 1.94]
Moderate(30≤ CL_{cr}<50)	6	1.95 [1.61, 2.35]	2.32 [1.85, 2.92]
Severe(CL_{cr}<30)	Five	2.86 [2.08, 3.94]	3.56 [2.51,5.06]

Subjects with normal renal function were included after considering the subject background according to the degree of renal dysfunction, and 8 subjects with normal renal function and those with severe renal dysfunction were mild and moderate renal dysfunction. In, 6 patients with normal renal function were compared with 6 patients, which was different from 8 patients with mild and moderate renal dysfunction.

***1: Creatinine clearance (mL / min)**

No clinical trials have been conducted in dialysis patients (including peritoneal dialysis). In addition, there is no data on the removal of this drug by dialysis (hemodialysis, peritoneal dialysis or hemofiltration).

Liver dysfunction

When a single oral dose of 1000 mg of this drug was given to 7 patients with moderate (Child-Pugh classification B) hepatic dysfunction, the minimum square geometric mean ratio of Imeglimin Cmax and AUC0-last (liver dysfunction).

The perpetrators / healthy adults) and 90% confidence intervals were 1.29 [1.05, 1.60] and 1.47 [1.19, 1.82], respectively (foreigner data).

Older people

In the Japanese late phase 2 and phase 3 studies in patients with type 2 diabetes, the steady-state AUC (AUC24, ss) of subjects who received 1000 mg of this drug orally twice daily was populated.

Estimated by ration PK analysis, AUC24, ss in the elderly aged 65 and over was 1.28 times that in the aged under 65.

4.5. Drugs interactions

This drug is mainly excreted as unchanged drug from the kidney

Precautions for combined use (Be careful about combined use).

Drug name, etc.	Clinical symptoms / measures	Mechanism / risk factors
Insulin preparation Sulfonylurea Fast-acting insulin secretagogue α-glucosidase inhibitor Thiazolidine drug DPP-4 inhibitor GLP-1 receptor agonist SGLT2 inhibitor, etc.	Be aware of the development of hypoglycemia. In particular, when used in combination with insulin preparations, sulfonylureas or fast acting insulin secretagogues, the risk of hypoglycemia may increase. To reduce the risk of hypoglycemia caused by these drugs, consider reducing the dose of insulin preparations, sulfonylureas, or fast acting insulin secretagogues.	The hypoglycemic effect may be enhanced.
Biguanide drugs	Be aware of the development of hypoglycemia and gastrointestinal symptoms.	For hypoglycemia, the hypoglycemia effect may be enhanced. Gastrointestinal symptoms tend to occur more often, especially in the early stages of concomitant use.
Drugs that enhance the hypoglycemic effect β-blockers Salicylic acid agents Monoamine oxidase inhibitors, etc.	Administer while carefully observing blood glucose level and other patient conditions.	The hypoglycemic effect may be enhanced.
Drugs that reduce hypoglycemic effects Adrenaline adrenocortical hormone thyroid hormone, etc.	Administer while carefully observing blood glucose level and other patient conditions.	The hypoglycemic effect may be enhanced.

If you have renal dysfunction, it is desirable to check renal function regularly because excretion of this drug may be delayed and blood concentration may increase.

Before using this drug, fully explain to patients the symptoms of hypoglycemia and how to deal with them.

Be careful when administering to patients who are engaged in work at heights, driving a car, etc., as they may cause hypoglycemic symptoms.

When administering, check blood glucose regularly to check the effect of the drug, and if the effect is insufficient after administration for 3 months, consider changing to a more appropriate treatment.

This drug and biguanide drugs may have a common mechanism of action, and when both drugs are used in combination, gastrointestinal symptoms occur compared to the combination therapy with other diabetic drugs. Care should be taken when selecting concomitant medications, as many have been observed.

4.6. Use in special population (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

The following patients or conditions that may cause hypoglycemia

Pituitary dysfunction or adrenal dysfunction

Malnutrition, starvation, irregular dietary intake, lack of dietary intake or weakness

Intense muscle exercise

Excessive alcohol intake

Patients with hepatic dysfunction

The blood concentration of this drug may increase.

In addition, clinical trials have not been conducted in patients with severe (Child-Pugh classification C) liver dysfunction.

Pregnant woman

Do not administer this drug to pregnant women or women who may be pregnant, and use insulin preparations. Transfer to the foetation has been observed in animal experiments (rats) 1). In animal experiments in which this drug was administered during the fetal organogenesis period, when 1500 mg / kg / day (corresponding to an exposure dose of about 17 times the maximum clinical dose of 2000 mg / day) was orally administered to rats. , Low surviving fetal body weight and delayed ossification have been observed 2). After implantation, when rabbits are orally administered at 200 mg / kg / day (corresponding to an exposure dose of about 1.4 times the maximum clinical dose of 2000 mg / day), total embryo absorption and the number of surviving foetus tend to be low. An increasing tendency of mortality and a low tendency of living fetal weight have been observed.

Lactating women

Consider continuing or discontinuing breastfeeding, taking into account the therapeutic benefits and benefits of breastfeeding. Transfer to milk has been observed in animal experiments (rats) 4).

Children

No clinical trials have been conducted on children.

Elderly

Carefully administer while observing the patient's condition. In general, physiological function is often reduced.

4.7. Effects on ability to drive and use machines

Since hypoglycemic symptoms may occur due to Imeglimin, if you feel dizzy while taking this medicine, do not drive or use machines.

4.8. Undesirable effects

Hypoglycemia (6.7%)

Hypoglycemia may occur. In particular, hypoglycemia may occur when used in combination with an insulin preparation, a sulfonylurea agent, or a fast-acting insulin secretagogue. If hypoglycemic symptoms (initial symptoms: weakness, severe hunger, sweating, etc.) are observed, take appropriate measures such as ingesting foods containing sugar. However, if hypoglycemic symptoms are observed in combination with an α-glucosidase inhibitor, glucose should be administered.

Other side effects/

	Less than 1 % to 5 %	**Less than 1 %**
Infectious diseases and parasites	-	Cystitis
Metabolic and malnutrition	-	Loss of appetite
Eye disorders	-	Diabetic retinopathy, diabetic retinal edema / macular edema
Gastrointestinal disorders	Nausea, diarrhea, constipation	Vomiting, abdominal discomfort, dyspepsia, upper abdominal pain, loose stools, abdominal distension, gastroesophageal reflux disease
Laboratory test	-	Increased blood lactate, increased lipase, weight loss

Information based on clinical use

It has been reported that biguanide drugs rarely cause serious lactic acidosis, and risk factors include renal dysfunction, hepatic dysfunction, hypoxic conditions, and dehydration (combination of diuretic drugs) (Including), excessive alcohol intake, infectious diseases, elderly people, etc. are known.

In nonclinical studies using rats, no clear effect on blood lactate concentration was observed with this drug, and no expression of lactic acidosis was observed in clinical studies, but this drug and biguanide drugs acted. Some of the mechanisms may be common.

Reporting of suspected adverse reactions

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

4.9. Overdose

There is no information available on Overdose.

5. Pharmacological properties

5.1. Mechanism of Action

Imeglimin is an investigational first-in-class novel oral agent for the treatment of type 2 diabetes (T2D). Several pivotal phase III trials have been completed with evidence of statistically significant glucose lowering and a generally favourable safety and tolerability profile, including the lack of

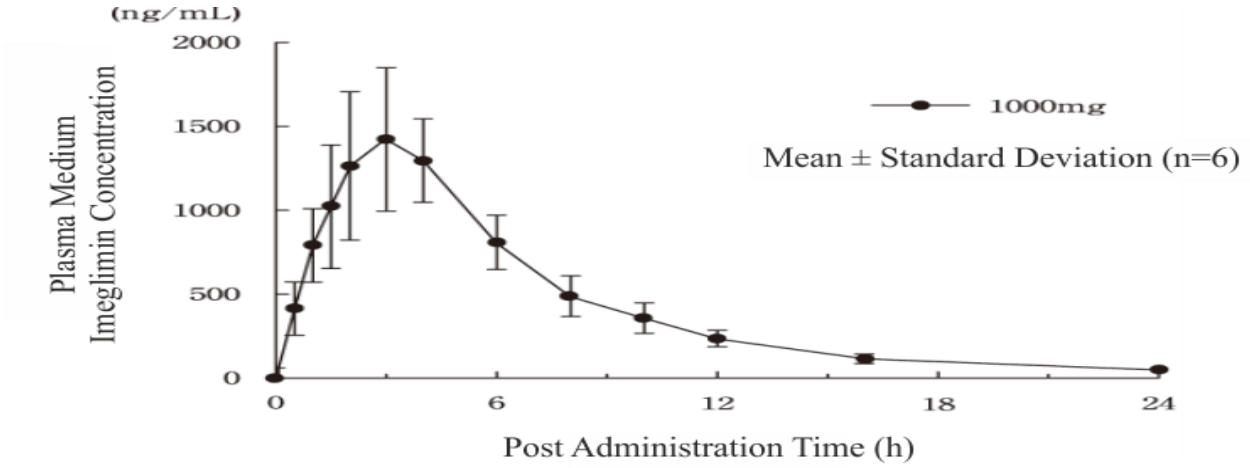
severe hypoglycaemia. Imeglimin's mechanism of action involves dual effects: (a) amplification of glucose-stimulated insulin secretion (GSIS) and preservation of β-cell mass; and (b) enhanced insulin action, including the potential for inhibition of hepatic glucose output and improvement in insulin signalling in both liver and skeletal muscle. At a cellular and molecular level, Imeglimin's underlying mechanism may involve correction of mitochondrial dysfunction, a common underlying element of T2D pathogenesis. It has been observed to rebalance respiratory chain activity (partial inhibition of Complex I and correction of deficient Complex III activity), resulting in reduced reactive oxygen species formation (decreasing oxidative stress) and prevention of mitochondrial permeability transition pore opening (implicated in preventing cell death). In islets derived from diseased rodents with T2D, Imeglimin also enhances glucose-stimulated ATP generation and induces the synthesis of nicotinamide adenine dinucleotide (NAD+) via the 'salvage pathway'. In addition to playing a key role as a mitochondrial co-factor, NAD+ metabolites may contribute to the increase in GSIS (via enhanced Ca++ mobilization). Imeglimin has also been shown to preserve β-cell mass in rodents with T2D. Overall, Imeglimin appears to target a key root cause of T2D: defective cellular energy metabolism. This potential mode of action is unique and has been shown to differ from that of other major therapeutic classes, including biguanides, sulphonylureas and glucagon-like peptide-1 receptor agonists.

5.2. Pharmacodynamic poperties

Blood concentration

Single dose

The changes in plasma concentration and pharmacokinetic parameters of a single oral dose of 1000 mg of this drug to healthy adults on an empty stomach were as follows



Dose	t_{max} (h)	C_{max} (ng/ mL)	AUC_{0-24} (ng·h/ mL)	$t_{1/2}$(h)
1000 mg (n = 6)	2.5 (1.5-3.0)	1393 (40.3)	9780 (36.1)	12.0 (113.0)

Repeated administration

When 1000 mg of this drug was orally administered twice daily to 6 healthy adults for 7 days, the plasma concentration reached a steady state on the 5th day of administration, and Cmax and AUC0-12 on the 7th day. The accumulation ratios were 1.43 times and 1.57 times, respectively.

As a result of population PK analysis based on plasma concentration obtained from 867 patients who received this drug, type 2 diabetic patients (103 patients: mean eGFR value 73.2 mL) enrolled

in a domestic phase 3 study (monotherapy) /Min/1.73M 2 weight exposure when this drug once 1000 mg was orally administered repeatedly twice daily) (AUC0-12, ss) was estimated to 18.0 μg · h / mL (geometric mean).

5.3. Pharmacokinetic properties

Absorption

Effect of diet

The pharmacokinetic parameters of a single oral dose of 1000 mg of this drug to healthy adult males on an empty stomach and after meals were as follows. No clinically significant dietary effects were observed.

Dosing time	t_{max} (h)	C_{max} (ng/ mL)	AUC_{0-48} (ng·h/ mL)	$t_{1/2}$(h)
On an empty stomach (n = 12)	3.0 (1.0- 4.0)	1681 (27.5)	12970 (30.6)	7.2 (56.4)
After meal (n = 12)	4.0 (3.0 - 4.0)	1424 (26.1)	11960 (29.9)	6.1 (59.9)

Distribution

The protein binding rate of Imeglimin in human plasma ranged from 1.2% to 6.4% 8) (*in vitro*).

Metabolism

When a single oral dose of 14 C-labeled Imeglimin 1000 mg was given to 6 healthy adult males , Imeglimin was hardly metabolized, and the main radioactive components in plasma and urine were unchanged 9) (foreigners).data). Imeglimin does not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4 / 5 (IC50 > 100 μ. mol/ L, CYP1A2, CYP2 at concentrations up to 120 μ. mol / L , CYP2C9, CYP2C19 and CYP3A4 / 5 were not induced 11) (*in vitro*).

Excretion

When a single oral dose of 14 C-labeled Imeglimin 1000 mg was given to 6 healthy adult men, the cumulative excretion rate of urinary radioactivity and unchanged drug up to 144 hours after administration was 43.2% and 42.0% of the administered radioactivity, and feces. The cumulative excretion rate of medium radioactivity was 54.8% of the administered radioactivity (foreigner data).

Imeglimin was a substrate for OCT1, OCT2, MATE1 and MATE2-K, but not for P-gp, BCRP, OAT1 and OAT3 (in vitro). Imeglimin showed no inhibitory effect on P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3 and MATE2-K (IC 50 > 1000 μ. mol / L) (in vitro).

On the other hand, it showed an inhibitory effect on OCT1 (K i: 154 μ. mol/ L), OCT2 (IC50: 146 μ. mol/ L) and MATE1 (IC50: 19.24 μ. mol/ L), but (in vitro), clinical problems. It was considered unlikely that a drug interaction would be observed.

The following pharmacokinetic parameters were calculated on data obtained from completed subjects for test and reference products.

Table 1: Summary of Pharmacokinetic Profile of Reference product (R)

Pharmacokinetic Parameter	N	Arithmetic Mean ± Standard Deviation	Coefficient of Variation	Median	Minimum	Maximum

C_{max} (ng/mL)	23	1537.5422± 530.0389	34.4731	1439.7150	883.1800	2760.1250
AUC_{0-t} (ng.hr/mL)	23	10750.3933 ±3769.0457	35.0596	9630.8934	5694.3162	20038.1314
$AUC_{0-\infty}$ (ng.hr/mL)	23	10994.5874 ±3769.2548	34.2828	9788.2965	5892.4316	20273.9605
t_{max} (hr)	23	2.5074±1.2 007	47.8878	2.6700	0.6700	4.0000
K_{el} (1/hr)	23	0.1794±0.0 256	14.2644	0.1785	0.1405	0.2435
$t_{1/2}$(hr)	23	3.9339±0.5 278	13.4166	3.8800	2.8500	4.9300
$AUC_{\_\%Extrap\_obs}$	23	2.4617±1.6 484	66.9626	1.9700	0.6900	7.7500

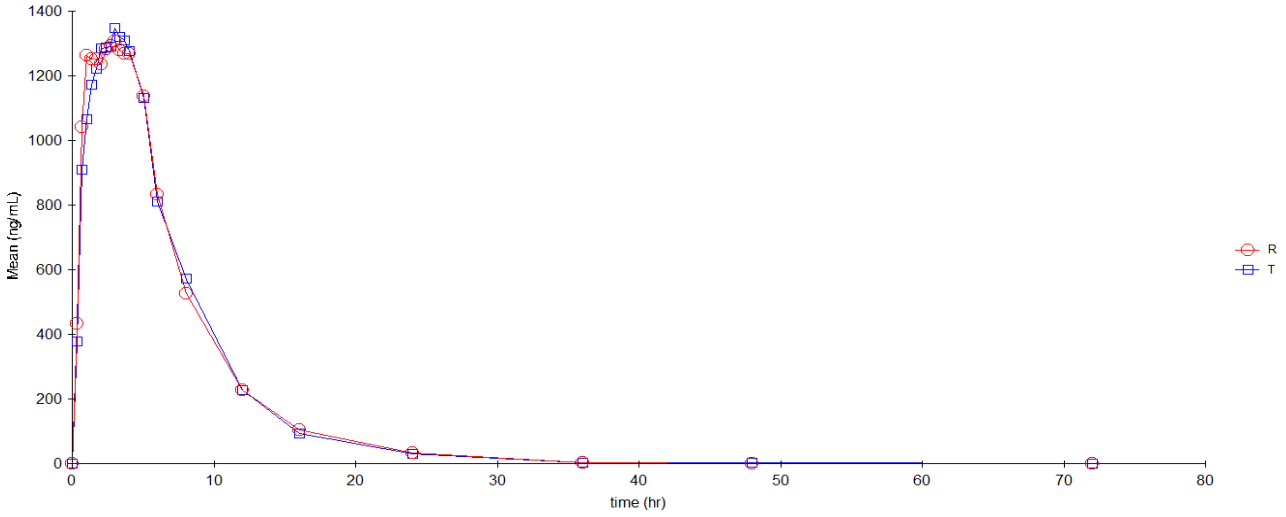
Table 2: Summary of Pharmacokinetic Profile of Test product (T)

Pharmacokinetic Parameter	N	Arithmetic Mean ± Standard Deviation	Coefficient of Variation	Median	Minimum	Maximum
C_{max} (ng/mL)	23	1546.8026± 415.3386	26.8514	1492.7290	711.7750	2405.6070
AUC_{0-t} (ng.hr/mL)	23	10693.0907 ±3732.9888	34.9103	10290.2470	4960.3306	18563.5017
$AUC_{0-\infty}$ (ng.hr/mL)	23	10932.0854 ±3688.1505	33.7369	10636.3106	5230.3066	18783.9839
t_{max} (hr)	23	2.8404±1.1 367	40.0199	3.0000	1.0000	5.0000
K_{el} (1/hr)	23	0.1868±0.0 511	27.3715	0.1884	0.0362	0.2936
$t_{1/2}$(hr)	23	4.4057±3.3 114	75.1615	3.6800	2.3600	19.1300
$AUC_{\_\%Extrap\_obs}$	23	2.6478±2.7 865	105.2380	1.7500	0.7600	14.4700

Table 3: Statistical Results of Log Transformed Test product (T) versus Reference product(R)

Pharmacokinetic Parameter	Geometric Least Square Mean		ISCV (%)	T/R Ratio (%)	Power (%)	90% Confidence Interval
	Test Product(T)	Reference Product(R)				
C_{max} (ng/mL)	1490.1200	1463.4701	23.06	101.82	88.87	90.71 TO 114.3
AUC_{0-t} (ng.hr/mL)	10066.457	10167.264	17.46	99.01	98.00	90.67 TO 108.12
$AUC_{0-\infty}$ (ng.hr/mL)	10347.041	10425.768	17.11	99.24	98.30	91.04 TO 108.19

Mean graph of Imeglimin HCl Tablets 1000 mg



Preclinical safety data

Sitagliptin

When 16 healthy adult males were co-administered 1500 mg of this drug once daily and 100 mg of sitagliptin once daily for 6 days, the AUCτ and Cmax of sitagliptin were 1.13 times and 1.15 times that of single administration.

Metformin

When this drug was administered to 15 healthy adult males at a dose of 1500 mg / dose and metformin at a dose of 850 mg twice daily for 6 days, the AUCτ and Cmax of metformin were 0.86 times and 0.90 times that of a single dose.

Cimetidine

When a single dose of 1500 mg of this drug and 400 mg of cimetidine were administered in combination to 16 healthy adults, the AUC0-last and Cmax of Imeglimin were 1.27 times that of the single dose.

Other drugs

In a study using population PK analysis, the AUC of Imeglimin when co-administered with other **diabetic drugs*** was estimated to be similar to the AUC when this drug was administered alone (estimated AUC ratio: 0.80 to 1.18).

***Diabetic drugs**

Sulfonylurea: Glycladide, Glimepiride

Fast-acting insulin secretagogue: Mitiglunide, lepaglutide

Biguanide: Metformin

α-glucosidase Inhibitor: Acarbose, Voglibose, Migitol

Thiazolidine: Pioglitazone

DPP-4 Inhibitor: Sitagliptin, Vildagliptin, Linagliptin, Teneligliptin

SGLT2 Inhibitors: Dapagliflozin, Empagliflozin

GLP-1 receptor agonists: lepaglutide

6. Nonclinical properties

6.1. Animal Toxicology or pharmacology

The acute oral median lethal dose (LD50) of Imeglimin HCL in Wistar rats & Swiss Albino mice was concluded as >2000.0 mg/kg body weight.

The repeated oral administration of Imeglimin HCl to male and female Wistar rats for a period of 28 days with 50.0 mg/kg, 100.0 mg/kg and 200.0 mg/kg body weight doses did not show any significant differences in the body weight, feed consumption and other parameters (male and female) as compared to vehicle control group. Hence, high dose of Imeglimin HCl (200.0 mg/kg, body weight) was concluded as NOAEL (No Observed Adverse Effect Level) in both male and female rats.

The repeated oral administration of Imeglimin HCl to New Zealand White Rabbits following a period of 28-days with 25.0 mg/kg, 50.0 mg/kg and 100.0 mg/kg body weight, doses did not show any significant differences in the body weight, feed consumption and other parameters of male and female rabbits as compared with vehicle control animals. Therefore, high dose of Imeglimin HCl (100.0 mg/kg, body weight) has been considered as NOAEL (No Observed Adverse Effect Level) in both male and female rabbits.

Non-Clinical Safety Data of Imeglimin Hydrochloride

All studies carried out to date on animals show that Imeglimin is very well tolerated in single doses (LD50 > 3,000 mg/kg) (LD50: average lethal dose) and after repeated administration with no major sign of toxicity.

Imeglimin has been administered orally for 26 weeks to rats and 52 weeks to dogs, and the dose with no adverse effect has been 250 mg/kg/d on rats and 300 mg/kg/d on dogs, yielding a very significant safety margin for administration of the product to humans.

Oral treatment with very high doses of Imeglimin of 1,000 and 1,500 mg/kg has been shown not to affect fertility in male or female rats.

Embryo-fetal toxicity studies have been carried out on rats up to a dose of 1,500 mg/kg and on rabbits up to a dose of 300 mg/kg. These studies have shown no sign of teratogenicity of Imeglimin.

Imeglimin has not shown any mutagenic potential in in vitro and in vivo studies.

There has been no evidence of hypersensitivity of the skin or eyes in the trials.

No signs of toxicity were observed on the central nervous systems, cardiac function or respiratory functions, apart from a slight decline in heart rate among three out of six dogs at a dose of Imeglimin of 500 mg/kg, during safety pharmacological studies. At this dose, the plasmatic exposure of Imeglimin in dogs is approximately 30 times greater than that observed in humans.

Efficacy and safety studies

Domestic late phase 2 study

A placebo-controlled, double-blind, controlled trial was conducted in patients with type 2 diabetes who had no experience of treating type 2 diabetes or who had received monotherapy with other

oral hypoglycemic agents for 12 weeks or longer. Patients treated with other oral hypoglycemic agents were discontinued at the time of screening, and after the washout period, this drug was administered at a dose of 500 mg, 1000 mg, 1500 mg or placebo twice daily. As a result of oral administration twice for 24 weeks, HbA1c was significantly decreased in all dose groups as compared with the placebo group as shown in the table below.

Administration group	**Number of cases *1**	**HbA1c (%)**		
		Average value before administration *2	Amount of change from before administration *3	Difference from placebo *3
placebo	75	7.89 ± 0.676	0.43 ± 0.092 [0.25, 0.61]	—
500 mg	75	7.94 ± 0.679	−0.09 ± 0.091 [−0.27, 0.09]	−0.52 ± 0.128 [−0.77, −0.27] p <0.0001
1000 mg	73	7.85 ± 0.650	−0.51 ± 0.093 [−0.69, −0.32]	−0.94 ± 0.129 [-1.19, −0.68] p <0.0001
1500 mg	73	7.91 ± 0.618	−0.57 ± 0.094 [−0.76, −0.39]	−1.00 ± 0.130 [−1.26, −0.75] p <0.0001

***1**: FAS group (fast-acting insulin secretagogue combination group)

***2**: Mean ± standard deviation

***3**: Analysis by Mixed Model Repeated Measures, least squares mean ± standard error [95% confidence interval]

The incidence of adverse drug reactions was 5.3% (4/75 cases) in the 500 mg group, 5.4% (4/74 cases) in the 1000 mg group, 24.0% (18/75 cases) in the 1500 mg group, and 8.0% (6/75 cases) in the placebo group. It was an example. Side effects with an incidence of 2% or more were not observed in the placebo group, 500 mg group, and 1000 mg group, and nausea 5.3% (4/75 cases), abdominal discomfort 5.3% (4/75 cases), and diarrhea 4.0% (4/75 cases) in the 1500 mg group. 3/75 cases) and vomiting 2.7% (2/75 cases). Hypoglycemia (symptomatic hypoglycemia and / or blood glucose level <70 mg / dL, and so on) was 1.3% (1/75 cases) in the 500 mg group, 1.4% (1/74 cases) in the 1000 mg group, and 1500 mg group. It was observed in 5.3% (4/75 cases) and 1.3% (1/75 cases) in the placebo group, but severe hypoglycemia Note 2) was not observed.

Domestic Phase 3 study (monotherapy)

A placebo-controlled, double-blind, controlled trial of type 2 diabetic patients who have not been treated for type 2 diabetes other than diet and exercise therapy or who have been receiving monotherapy with other oral hypoglycemic agents for 12 weeks or longer. Carried out. Patients treated with other oral hypoglycemic agents were discontinued from oral hypoglycemic agents at the time of screening, and after the washout period, 1000 mg of this drug or placebo was orally administered twice daily for 24 weeks. As shown, HbA1c was significantly decreased in the riociguat group compared with the placebo group.

Administration group	No. of cases ※1	HbA1c (%)		
		Average value before administration ※2	Amount of change from before administration ※3	With placebo difference ※3
placebo	106	7.93±0.684	0.15±0.07 [0.008, 0.286]	—
This drug	106	7.99±0.764	−0.72±0.07 [−0.856, −0.581]	−0.87±0.09 [−1.041,−0.691] p<0.0001

※1: FAS group (fast-acting insulin secretagogue combination group)

※ 2: Average ± standard deviation

※3: Analysis by Mixed Model Repeated Measures, least squares average ± Standard error [95% confidence interval].

Clinical Studies

A total of 238 patients were screened out of which 216 patients were randomized by computer generated randomization program to either of the study arm i.e., Imeglimin Hydrochloride tablets 1000 mg (Arm A) or Placebo Tablets (Arm B) in 2:1 proportion. Total patients randomized/enrolled were 144 in Imeglimin Hydrochloride Tablets 1000 mg arm and 72 in Placebo Tablet arm. All sites had approval from the respective Institutional Ethics Committees prior to the study initiation.

Imeglimin Hydrochloride Tablets 1000 mg were produced statistically significant reductions in HbA1c, fasting plasma glucose & 2-hour post prandial glucose from baseline to end of the study visit.

For evaluation of safety, frequency of suspected, unanticipated adverse drug reactions reported possibly related to the investigational product up to end of study from start of the treatment was considered. Safety and tolerability of the test and reference products were assessed depending on the outcome from this clinical study. There were events and evidence of adverse reaction observed but was nonsignificant. Total 47 AEs were reported in 47 patients. 29 AEs were reported in Imeglimin Hydrochloride Tablets 1000 mg arm and 18 AEs were reported in Placebo Tablets arm. 05 AEs from Imeglimin Hydrochloride Tablets 1000 mg arm and 02 AEs from Placebo Tablets arm were moderate in nature; all the other AEs were mild in nature. No SAE was reported during the study.

	Imeglimin Hydrochloride Tablets 1000 mg (N=144)	Placebo Tablets (N=72)	Total (N=216)
Number of Events/Participants			
Number of Adverse Events	29	18	47
Participants with at least one AE	29	18	47
Number of SAEs	00	00	00
Participants with at least one SAE	00	00	00
Severity (All AEs)			
Mild	24	16	40

Moderate	05	02	07
Severe	00	00	00

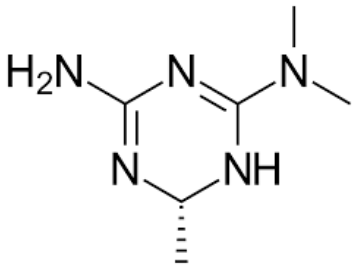
Summary of Adverse Events by Enrolment Group

Imeglimin Hydrochloride Tablets 1000 mg significantly improved HbA1c in patients with type 2 diabetes mellitus compared with placebo and had a similar safety profile to placebo. Imeglimin Hydrochloride Tablets 1000 mg represents a potential new treatment option for patients with type 2 diabetes mellitus.

7. Description

Imeglimin Hydrochloride:

Imeglimin Hydrochloride is (4R)-6-N,6-N,4-trimethyl-1,4-dihydro-1,3,5-triazine-2,6-diamine;hydrochloride The empirical formula is $C_6H_{13}N_5$ and its molecular weight is 191.66 g/mol. The chemical structure is:



IMEXTOR

Imeglimin Hydrochloride Sustained Release Tablets are White, Capsule shape, biconvex, film coated tablets, plain on both sides.The Excipients used are Microcrystalline Cellulose, Povidone, Colloidal Silicon dioxide, Hydroxypropylmethyl Cellulose, Microcrystalline Cellulose, Colloidal Silicon dioxide, Magnesium Sterate, Instacoat universal white

8. Pharmaceutical particulars

8.1. Incompatibilities

Not applicable

8.2. Shelf-life

Do not use later than date of expiry.

8.3. Packaging information

IMEXTOR SR 500/1000 is available in pack of 10 Tablets.

8.4. Storage and handing instructions

Store below 30^{O} C. Protected from light.

Keep out of reach of children.

Do not chew or crush the tablet.

Swallow as whole.

9. Patient Counselling Information

Ask the patients to inform the treating physicians in case of any of the below:

- Have any allergies

- Have kidney or liver problems
- Are pregnant or plan to become pregnant
- Are breastfeeding or plan to breastfeed
- Have any serious illness
- Are taking any medicines (prescription, over-the-counter, vitamins, or herbal products)

10. Details of manufacturer

Exemed Pharmaceutics

Plot No. 133/1 & 133/2, G.I.D.C.,

Selvas Road, Vapi-396 195,

Dist.: Valsad, State: Gujarat, India.

11. Details of permission or license number with date

Mfg. Licence No: G/25/2011 Issued on: 25.01.2024.

12. Date of revision

Not Applicable

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/ IMEXTOR SR (500/1000) /JUN-24/01/PI