For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

IMEXTOR

1. GENERIC NAME

Imeglimin Hydrochloride Tablets 500 and 1000 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Film Coated Tablet Contains

Imeglimin Hydrochloride…….500/1000 mg

Excipients……q.s

The excipients used are Povidone, Microcrystalline cellulose, Croscarmellose Sodium, Colloidal silicone dioxide, Magnesium Stearate, Hypromellose, Polyethylene Glycol.

3. DOSAGE FORM AND STRENGTH

Dosage form: Film Coated Tablets

Strength: 500 mg and 1000 mg

4. CLINICAL PARTICULARS

4.1 Therapeutic Indication

It is indicated for type 2 diabetes mellitus.

4.2 Posology and Method of Administration

In general, for adults, 1000 mg of Imeglimin hydrochloride is orally administered twice daily in the morning and evening.

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.

4.3 Contraindications

- Patients with a history of hypersensitivity to the ingredients of this drug.
- Patients with severe ketosis, diabetic coma or diabetic precoma, type 1 diabetes [immediate correction of hyperglycemia with transfusion and insulin is essential].
- Patients with severe infection, before or after surgery, or with serious trauma [Since blood sugar 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. No clinical trials have been conducted in patients with moderate or severe renal dysfunction (eGFR < 45 mL / min / 1.73 m2) using efficacy and safety as indicators, and administration is not

recommended.

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
Diabetes drug 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 Populations (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 renal dysfunction

Patients with renal dysfunction with eGFR < 45 mL / min / 1.73 m 2 (including dialysis patients)

Administration is not recommended. The blood concentration of this drug may increase significantly

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 side effects

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.

By reporting side effects, you can help provide more information on the safety of this medicine.

4.9 Overdose

Not available

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of action

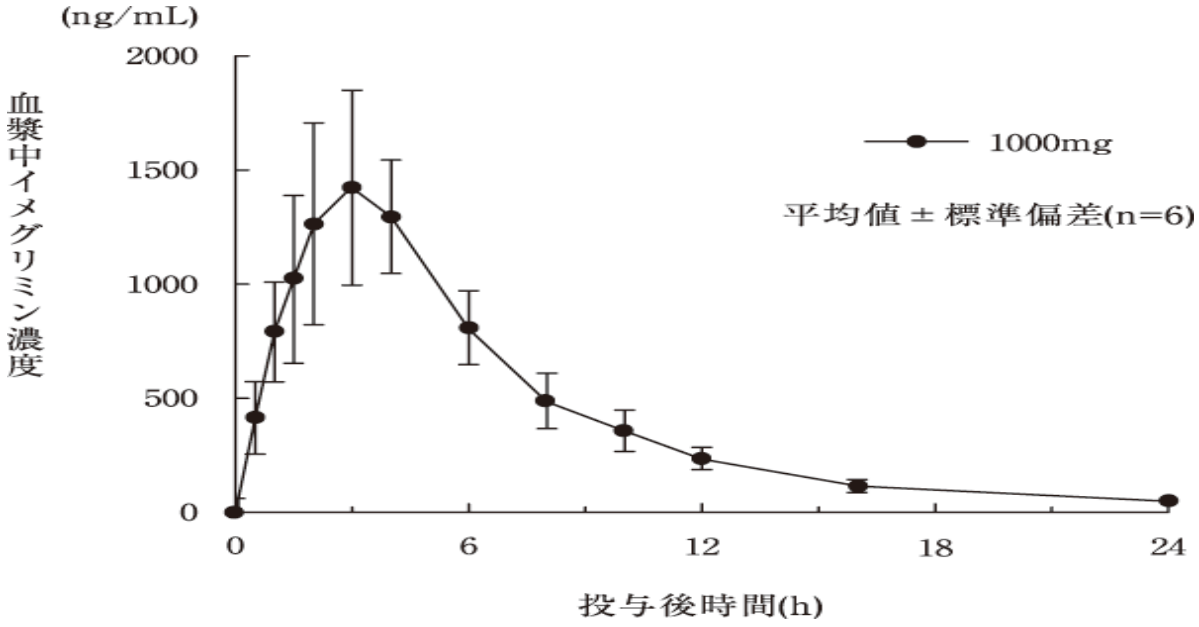
Imeglimin is a drug that exerts a hypoglycemic effect through a glucose leveldependent insulin secretion-promoting effect and an insulin resistance-improving effect, and its mechanism of action is presumed to be via an action on mitochondria.

5.2 Pharmacodynamic Properties

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±1.2007	47.8878	2.6700	0.6700	4.0000
K_{el} (1/hr)	23	0.1794±0.0256	14.2644	0.1785	0.1405	0.2435
$t_{1/2}$(hr)	23	3.9339±0.5278	13.4166	3.8800	2.8500	4.9300
$AUC_{\_\%Extrap\_obs}$	23	2.4617±1.6484	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±1.1367	40.0199	3.0000	1.0000	5.0000
K_{el} (1/hr)	23	0.1868±0.0511	27.3715	0.1884	0.0362	0.2936
$t_{1/2}$(hr)	23	4.4057±3.3114	75.1615	3.6800	2.3600	19.1300

$AUC_{\_\%Extrap\_obs}$	23	2.6478±2.7865	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

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	No. of	HbA1c (%)

group	cases ※1	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

	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

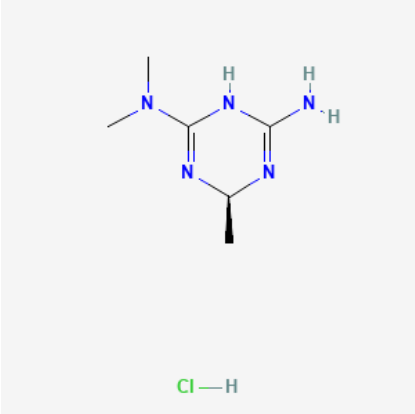
considered. Safety and tolerability of the test and reference products were assessed depending on the outcome from this clinical study. There were events and evidence of adverse reaction observed but was nonsignificant. Total 47 AEs were reported in 47 patients. 29 AEs were reported in Imeglimin Hydrochloride 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.

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 is (4R)-6-N,6-N,4-trimethyl-1,4-dihydro-1,3,5-triazine-2,6-diamine;hydrochloride. The molecular formula is C6H14ClN5 and the molecular weight is 191.66. The chemical structure of Imeglimin Hydrochloride is:



IMEXTOR 500

Imeglimin Hydrochloride Tablets 500 mg are white to off white, round, biconvex, film coated tablets, plain on both sides. The excipients used are Povidone, Microcrystalline cellulose, Croscarmellose Sodium, Colloidal silicone dioxide, Magnesium Stearate, Hypromellose, Polyethylene Glycol.

IMEXTOR 1000

Imeglimin Hydrochloride Tablets 1000 mg are white to off white, capsule shape, biconvex, film coated tablets, plain on both sides. The excipients used are Povidone, Microcrystalline cellulose, Croscarmellose Sodium, Colloidal silicone dioxide, Magnesium Stearate, Hypromellose, Polyethylene Glycol.

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 is available in blister strip of 10 tablets each.

8.4 Storage and Handing Instructions

Store below 30°C

9. PATIENT COUNSELLING INFORMATION

IMEXTOR 500 and 1000mg film-coated tablets

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again

. • If you have any further questions, ask your doctor or pharmacist.

- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

9.1 What IMEXTOR is and what it is used for

9.2 What you need to know before you use IMEXTOR

9.3 How to use IMEXTOR

9.4 Possible side effects

9.5 How to store IMEXTOR

9.6 Contents of the pack and other information

9.1 What IMEXTOR is and what it is used for

Imeglimin Hydrochloride is a first-in-class drug with a unique dual mechanism of action for the treatment of Type 2 Diabetes across the continuum of the current treatment paradigm, both as a monotherapy or as an add-on to other glucose lowering therapies. Imeglimin is a drug that exerts a hypoglycemic effect through a glucose level-dependent insulin secretion-promoting actions and insulin resistance-improving effects, and its mechanism of action is presumed to be via action on mitochondria.

9.2 What you need to know before you take IMEXTOR

Do not take IMEXTOR:

If you are allergic to Imeglimin or any of the other ingredients of this medicine & If you think you may be allergic to Imeglimin or any of the other ingredients of Imeglimin.

Patients with complications / medical history

- 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 renal dysfunction

Patients with renal dysfunction with eGFR < 45 mL / min / 1.73 m 2 (including dialysis patients)

Administration is not recommended. The blood concentration of this drug may increase significantly.

➢ 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.

Other medicines and Imeglimin Tablets:

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Your doctor may wish to alter your dose of Imeglimin Tablets if you are taking other medicines such as:

Diabetes drugs, Insulin preparations, Sulfonylurea, Fast-acting insulin secretagogue α-glucosidase inhibitor, Thiazolidine drug, DPP-4 inhibitor, GLP-1 receptor agonist SGLT2 inhibitor, etc.

Biguanide drugs

Drugs that enhance the hypoglycemic effect: β-blockers Salicylic acid agents, Monoamine oxidase inhibitors, etc.

Drugs that reduce hypoglycemic effects: Adrenaline adrenocortical hormone thyroid hormone, etc.

Pregnancy, breast feeding and fertility

If you are pregnant or breast-feeding, don't take this medication.

Driving and using machines

If you feel dizzy while taking this medicine, do not drive or use machines.

9.3 How to take IMEXTOR

Adults

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure. Swallow the tablet whole with some water.

If you take more Imeglimin Tablets than you should

If you have taken too many tablets, contact your doctor immediately or go to the nearest hospital casualty department taking any remaining medication and this patient information leaflet with you.

If you forget to take Imeglimin Tablets

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.

9.4 Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Stop taking this medicine and consult your doctor immediately if any of the following occur Hypoglycemia, Vomiting, abdominal discomfort, dyspepsia, upper abdominal pain, loose stools, abdominal distension, gastroesophageal reflux disease, cystitis, Diabetic retinopathy, diabetic retinal edema / macular edema, increased blood lactate, increased lipase and weight loss you may need medical treatment.

Reporting of side effects

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.

By reporting side effects, you can help provide more information on the safety of this medicine.

9.5 How to store IMEXTOR

Store below 30°C

9.6 Contents of the pack and other information.

IMEXTOR is available in blister pack of 10 tablets

10. DETAILS OF MANUFACTURER

Manufactured by:

M/s. Exemed Pharmaceuticals

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

Selvas Road, Vapi – 396195,

Dist.: Valsad, Gujarat, INDIA

11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

Mfg. Lic. No: G/25/2011 issued on 11.10.2022

12. DATE OF REVISION

NA

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/ IMEXTOR 500 mg, 1000 mg/Dec 2022 /01/PI