PRESCRIBING INFORMATION

Imeglimin Hydrochloride 500mg Film Coated Tablet

1. Generic Name

Imeglimin Hydrochloride 500mg Film Coated tablet

2. Qualitative and quantitative composition

Each Film Coated tablets contains:

Imeglimin Hydrochloride …….. 500mg

3. Dosage form and strength

Film Coated Tablets

4. Clinical particulars

4.1 Therapeutic indication

Type 2 Diabetes Mellitus.

4.2 Posology and method of administration.

Posology: As directed by R.M.P

Method of Administration: To be taken orally

4.3 Contraindications

IMEGLIMIN:

- Patients with a history of hypersensitivity reaction to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

IMEGLIMIN:

"WARNING: To be sold by retail only under the prescription of Endocrinologists or internal medicine specialists only"

- Strictly follow the instructions on dietary/exercise therapy.
- If you experience hypoglycemic symptoms (hungry, cold sweat, pale face, easy tiredness, tremor of limbs, convulsions, decreased consciousness, etc.), take foods containing sugar or sugar in general.
- Follow your doctor's instructions and take regular blood tests.

4.5 Drugs interactions

IMEGLIMIN:

There was no evidence that it had the potential to cause cytochrome P450 inhibition or induction. It was shown to be a substrate of organic cation transporter (OCT) 1, OCT2, multidrug and toxin

extrusion (MATE) 1, and MATE2-K and an inhibitor of OCT1, OCT2, and MATE1; as a consequence, corresponding clinical drug-drug interaction studies were performed and confirmed the absence of relevant interactions with substrates or inhibitors of these transporters.
Imeglimin is a substrate of MATE2-K and also a substrate and an inhibitor of OCT1, OCT2, and MATE1 transporters; however, there are no clinically significant interactions when Imeglimin is co-administered with either a substrate or an inhibitor of these transporters.

CYP inhibition studies

The results of these studies indicated that Imeglimin does not appear to cause any substantial direct inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5. The IC50 values for these enzymes were greater than the highest concentration of Imeglimin studied (up to 1000 μM and up to 6000 μM for CYP3A4). Furthermore, there was little or no evidence that Imeglimin has the potential to cause time-dependent inhibition of any of the CYP enzymes evaluated.
In terms of the drug-drug interaction profile, there is little or no evidence suggesting that Imeglimin has the potential to cause metabolism-dependent DDI as Imeglimin is poorly metabolized and has no inhibition potential towards CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5 (up to 1000 μM for all CYPs and up to 6000 μM for CYP3A4/5). These concentrations largely covered the maximal clinical plasma concentration observed at steady state, ~10 μM, and the Imeglimin intestinal concentration potentially leading to an inhibition of intestinal CYP3A4/5: 3mM. Moreover, Imeglimin did not display inducing effects on CYP1A2, CYP2B6 or CYP3A4. Since the highest concentration tested, 120 μM, is about 16-fold higher than Cmax observed in the clinical ADME study (1432 ng/mL = 7.5 μM), Imeglimin can be considered unlikely to induce CYP in clinical settings even if a potential induction of intestinal CYP3A4 cannot be formerly ruled out.

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

- If you have previously experienced any allergic reactions (itch, rash, etc) to any medicines or foods.
- If you are in a state of ketosis, in a diabetic coma/precoma, in perioperative period, or injured.
- If you have type 1 diabetes or infections.
- If you are pregnant or breastfeeding.
- If you are taking any other medicinal products. (Some medicines may interact to enhance or diminish medicinal effects. Beware of over-the-counter medicines and dietary supplements as well as other prescription medicines.)

4.7 Effects on ability to drive and use machines

Driving and use of machines

This medicine may cause hypoglycemic symptoms. Therefore, pay close attention when you work at heights, drive a car, or operate dangerous machinery.

4.8 Undesirable effects
IMEGLIMIN:

- The most commonly reported adverse reactions include nausea, diarrhea and constipation. If any of these symptoms occur, consult with your doctor or pharmacist.
- Weakness, hungry feeling, sweating [hypoglycemia].

4.9 Overdose
IMEGLIMIN:
Preclinical studies have demonstrated a glucose-independent insulinotropic effect of IMEG at supratherapeutic doses, which raises concerns about overdosing and the associated risk of hypoglycaemia if dosing is inappropriate, in patients with renal (or hepatic) impairment and in patients with increased sensitivity to IMEG.

5. Pharmacological properties
5.1 Mechanism of Action
IMEGLIMIN:
Imeglimin has a unique and original mechanism of action that targets mitochondrial bioenergetics. Mitochondria are the cells' energy centers and are directly involved in the genesis of type 2 diabetes, a disease that essentially involves an imbalance between overeating and a lack of physical activity.
Imeglimin is the first representative of a new class of oral anti-diabetics, glimins. This class was recognized by the World Health Organization in 2007. It includes treatments for type 2 diabetes targeting mitochondrial bioenergy (as described in "Imeglimin mechanism of action: regulating mitochondrial bioenergy to act on the three diabetes key effects and protect patients from their complications"). Imeglimin is a small, chemical synthesis molecule belonging to the tetrahydrotriazine family, with an original mechanism of action that targets the mitochondria.
A number of preclinical studies have been performed to show that Imeglimin is able to regulate mitochondrial bioenergetics by counteracting the mitochondrial dysfunction responsible for the diabetes pathology and its micro- and macrovascular complications.
The mitochondria are the power stations of cells, contributing to the regulation of energy balance, and thus metabolism. The principal role of mitochondria is to produce energy in the form of an ATP (adenosine triphosphate) molecule, by oxidizing nutrients (glucose and fatty acids) from food. The functioning of mitochondria and their bioenergetics equilibrium can be monitored by function gauges. In simplified way, these gauges include the following parameters:

- **Redox potential:** it is dependent of nutrient supply - the greater the supply, the more the cell's oxidized state increases;

- **Reactive derivatives of oxygen ROS (reactive oxygen species):** the greater the mitochondrial functioning, the greater the production of ROS. Overproduction of ROS aggravates mitochondrial dysfunction;
- **Membrane potential:** this increases when energy demand is low (sedentary lifestyle) and **nutrient** supply is high (excess food);
- **The ATP/ADP ratio:** this ratio quantifies the cell's energy status, which guides mitochondria function. If it is low, the mitochondria will function at full speed, and if high the mitochondria will slow down.

  In the physiopathology of diabetes, food excess and sedentarity lifestyle output lead to a disequilibrium in the energy balance linked to the fact that the supply is higher than demand. This disequilibrium will create pressure on the mitochondria, resulting in increased membrane potential. This pressure on the mitochondria will also cause an increase in the production of ROS, a higher oxidized state. The function gauges will then pass into an alert zone. In a situation of disequilibrium of the energy balance, Imeglimin is capable of regulating the functioning of these mitochondrial gauges and bringing them into a normal functioning zone. Imeglimin, therefore, will be able to reduce the pressure applied on the mitochondria and restore their normal functioning. Through this mitochondrial action, Imeglimin will restore the organs' sensitivity to glucose and insulin, leading to the following:

- an increase in glucose-dependent insulin secretion by the pancreas
- a decrease in the excess production of glucose by the liver
- an increase in the uptake and use of glucose by the muscles

5.2 Pharmacodynamic properties

IMEGLIMIN:

Inhibition of hepatic glucose production

Imeglimin has shown an inhibitory effect in glucose production in both isolated rat liver cells and rat liver slices.4,5 Moreover, imeglimin elicited a reduction in glucose produced by the isolated cells in a concentration-dependent pattern, with reductions ranging from 9% (for 0.25 mmol/L) to 80% (for 1.5 mmol/L), which is comparable to the results of metformin in its highest dosages.7 In liver slices, the inhibition of glucose production was also apparent; in a dose-dependent pattern, the reduction ranged from 14% (for 2.5 mmol/L) to 84% (for 10 mmol/L).5 On a molecular level, imeglimin achieved these results by downregulating phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase) in isolated hepatocytes from rats, and by inhibiting lactic acidosis via the mitochondrial-dependent pathway.

Stimulation of skeletal muscle glucose uptake

In muscle cell cultures, imeglimin has shown effectiveness by inducing glucose uptake by the muscle cells, which was statistically significant at a dose of 0.5 mmol/L ($p<0.01$), with up to a 3.3-fold increase at the maximum dose given (2 mmol/L), compared with control. In vivo, in soleus and gastrocnemius muscle from streptozotocin diabetic rats, imeglimin showed a statistically

significant ($p<0.01$) increase in glucose uptake even at the lowest dose (25 mg/kg), restoring the uptake to normal for diabetic rats at 50 mg/kg and 100 mg/kg ($p<0.05$, and $p<0.01$ respectively). There are various proposed molecular pathways for the action of imeglimin on insulin sensitivity, even though they are not fully understood. One proposed way is the increase in Akt (protein kinase B) phosphorylation, which passes the insulin signal transduction; another possible pathway might include glucose transporter-4 expression and the regulation of insulin receptor substrate phosphorylation.

5.3 Pharmacokinetic properties

IMEGLIMIN:

Absorption:

Imeglimin is a small cationic compound with an intermediate intestinal permeability. Its absorption mechanism involves an active transport process in addition to passive paracellular absorption. Absorption was good (50-80%) in vivo across several species but decreased with increasing dose probably due to a saturation of active transport.

Distribution:

After absorption, imeglimin was rapidly and largely distributed to internal organs. Plasma protein binding was low which can explain the rapid distribution to organs observed in all species.

Biotransformation

In animals and humans, imeglimin was largely excreted unchanged in urine, indicating a low extent of metabolism. Unchanged drug was the main circulating entity in plasma and none of the identified metabolites were unique to human.

Elimination

Imeglimin renal clearance (CLR) was higher than creatinine clearance indicating that it was actively secreted into urine. There was no evidence that it had the potential to cause cytochrome P450 (CYP450) inhibition or induction. It was shown to be a substrate of Organic Cation Transporter 1 (OCT1), OCT2, Multidrug and toxin extrusion 1 (MATE1) and MATE2-K and an inhibitor of OCT1, OCT2 and MATE1; as a consequence, corresponding clinical drug-drug interaction studies were performed and confirmed the absence of relevant interactions with substrates or inhibitors of these transporters.

6. Nonclinical properties

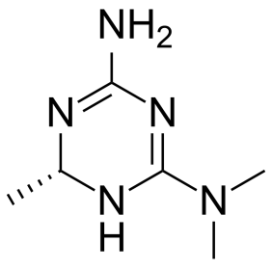
6.1 Animal Toxicology or Pharmacology

Not required.

7. Description

Imeglimin has a unique and original mechanism of action that targets mitochondrial bioenergetics. Mitochondria are the cells' energy centers and are directly involved in the genesis of type 2 diabetes, a disease that essentially involves an imbalance between overeating and a lack of physical activity.

Imeglimin is the first representative of a new class of oral anti-diabetics, glimins. This class was recognized by the World Health Organization in 2007. It includes treatments for type 2 diabetes targeting mitochondrial bioenergy (as described in "Imeglimin mechanism of action: regulating mitochondrial bioenergy to act on the three diabetes key effects and protect patients from their complications"). Imeglimin is a small, chemical synthesis molecule belonging to the tetrahydrotriazine family, with an original mechanism of action that targets the mitochondria:



8.Pharmaceutical particulars

8.1 Incompatibilities

No incompatibility study has been found.

8.2 Shelf-life

12 Months

8.3 Packaging Information

1X10 Alu-Alu Blister

8.4 Storage

Store below 30℃ & Protect from Light & Moisture.

9. Patient Counselling Information

IMEGLIMIN:

- If you have previously experienced any allergic reactions (itch, rash, etc.) to any medicines or foods.
- If you are in a state of ketosis, in a diabetic coma/precoma, in perioperative period, or injured.
- If you have type 1 diabetes or infections
- If you are pregnant or breastfeeding.
- If you are taking any other medicinal products. (Some medicines may interact to enhance or diminish medicinal effects. Beware of over-the-counter medicines and dietary supplements as well as other prescription medicines.).

Other General Warnings

Talk to your doctor if

- ➢ You experience any allergic reactions after taking Imeglimin.
- ➢ You have any pre-existing medical conditions such as heart disorder, liver or kidney problem, thyroid, etc.

- You are getting suicidal thoughts after taking this medicine, talk to your doctor immediately.
- You are experiencing vision problems or dizziness and sleepiness.

10. Details of manufacturer

Synokem Pharmaceuticals Ltd.

Plot No. 35-36, Sector-6A, Integrated Industrial Estate (SIDCUL), Ranipur, (BHEL), Haridwar-249403 (Uttarakhand)

11. Details of permission or licence number with date:

MF-ND-102/2022, Dated – 28-Oct-2022

12. Date of revision

03.11.2022