SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the Medicinal Product:

Neomet Tablets 1000 mg

2. Qualitative & Quantitative Composition:

Each tablet contains 1000 mg Metformin Hydrochloride BP.

3. Pharmaceutical Form:

Film-coated tablet

4. Clinical Particulars:

4.1 Therapeutic indications

Neomet is prescribed by your doctor as an addition to diet and exercise to improve glycaemic control in patients with Type 2 diabetes.Neomet may also be prescribed along with another oral antidiabetic drug belonging to other groups like sullonylureas, thiazolidines, meglitinides or insulin to improve glycaemic control.

4.2 Posology and method of administration

Posology

The dosage of Neomet is prescribed on an individual basis according to the blood glucose measurements.

Use in adults:

The usual starting dose of Neomet is one to two 500 mg tablets or one 850 mg tablet daily with meals. The maximum dose is 2 g per day given in divided doses. Neomet should not be crushed *or* chewed but swallowed as a whole.

Use in children:

Neomet is not recommended in children below 10 years of age. For Children of 10 years and above, the usual starting dose of Neomet is 500 mg twice a day, given during or after meals

Dosage increases should be made in increments of 500 mg weekly upto a maximum of 2 g per day given in divided doses.

4.3 Contraindications

Hypersensitivity to metformin hydrochloride or to any of the excipients.

- Diabetic ketoacidosis, diabetic pre-coma.
- Renal failure or renal dysfunction (creatinine clearance < 60 ml/min).
- Acute conditions with potential to alter renal function such as:
  - Dehydration,
  - Severe infection,
  - Shock,
  - Intravascular administration of iodinated contrast agents.
- Acute or chronic disease which may cause tissue hypoxia such as:
  - Cardiac or respiratory failure,
    Recent myocardial infarction,
  - Shock
- Hepatic insufficiency, acute alcohol intoxication, alcoholism
- Lactation.

4.4 Special warning & precautions for use

Care should be taken for the following condition before taking Neomet:

- Allergic to metformin
- diabetic ketoacidosis
- diabetic precoma
- renal failure or renal dysfunction
- liver problems
- heart failure that is being treated with medicines
- persistent diarrhoea, repeated vomiting
- undergoing a surgery
- X-ray that involves injection with dyes
- 80 years and older and have not undergoing kidney function test
- Excess alcohol consumption
- Pregnant mother

Breastfeeding mother

4.5 Interaction with other medicinal products & other forms of interaction

Certain drugs that are excreted through the kidney, theoretically, have the potential to interact with Neomet.

Care should be taken if a patient is uder following medication:

- Amiloride	- Quinidine	- Triamterene	– Procainamide
- Digoxin	- Quinine	– Trimethoprim	
- Morphine	- Ranitidine	- Vancomycin	

The following drugs possibly enhance the hypoglycaemic effects of metformin: ACE inhibitors, anabolic steroids, monoamine oxidase inhibitors.

The following drugs may possibly antagonise the hypoglycaemic effects of metformin: diazoxide, loop diuretics and thiazides and relative diuretics, oestrogens, progestogens.

In patients who are on treatment with metformin and ketotifen, the administration of antihistamines may depress the thrombocyte count.

Warning signs (such as tremor) with antidiabetics may be masked when given with a group of drugs called beta blockers.

The hypoglycaemic effects of antidiabetics are possibly enhanced by testosterone.
Cimetidine reduces the excretion of metformin.

Aminoglutethimide may possibly accelerate the metabolism of biguanides such as metformin.

4.6 **Pregnancy and Lactation**

The use of Neomet is not recommended in pregnancy and breastfeeding.

The doctor should be informed if a patient is pregnant, planning to become pregnant or is a breastfeeding mother.

4.7 Effects on ability to drive & use machines

Metformin hydrochloride monotherapy does not cause hypoglycemia and therefore has no effect on the ability to drive or to use machines.

However, patients should be alerted to the risk of hypoglycemia when metformin hydrochloride is used in combination with other antidiabetic agents (sulfonylureas, insulin, repaglinide).

4.8 Undesirable Effects

The most common side effects are relevant to the gastrointestinal tract. They include diarrhoea, nausea, vomiting, flatulence, indigestion, and abdominal discomfort. Other side effects include headache, light-headedness, asthenia, breathlessness, skin rash, nail disorder, chest discomfort, chills, flu syndrome, flushing and irregular heartbeat.

In rare cases, Neomet can cause a serious side effect called lactic acidosis. In this condition, the lactic acid levels in the blood go up and this can cause serious damage. This condition has mostly occurred in those patients whose kidneys are not functioning normally. It is also important that the liver is functioning normally as it helps remove lactic acid from the blood.

If the following signs of lactic acidosis occur, an immediate medical emergency treatment is required.

- feeling very weak, tired or uncomfortable
- unusual muscle pain
- difficult Breathing
- unusual stomach discomfort
- feeling cold
- dizziness or light-headedness
- sudden slow and irregular heart beat

4.9 Overdose

Hypoglycaemia has not been seen with metformin hydrochloride doses of up to 85 g, although lactic acidosis has occurred in such circumstances. High overdose of metformin hydrochloride or concomitant risk may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be

treated in hospital. The most effective method to remove lactate and metformin hydrochloride is haemodialysis.

5. Pharmacological Properties:

5.1. Pharmacodynamics:

Pharmacotherapeutic group: Blood glucose lowering drugs. Biguanides; ATC code: A10BA02
Metformin is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

Metformin may act via 3 mechanisms:
reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis.
in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilization.
and delay of intestinal glucose absorption.
Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase.
Metformin increases the transport capacity of all types of membrane glucose transporters (GLUTs) known to date.
In clinical studies, use of metformin was associated with either a stable body weight or modest weight loss.

In humans, independently of its action on glycaemia, metformin has favourable effects on lipid metabolism.

This has been shown at therapeutic doses in controlled, medium-term or long- term clinical studies: metformin reduces total cholesterol, LDL cholesterol and triglyceride levels.

Clinical efficacy:

The prospective randomised study (UKPDS) has established the long-term benefit of intensive blood glucose control in adult patients with type 2 diabetes.

Analysis of the results for overweight patients treated with metformin after failure of diet alone showed:

- a significant reduction of the absolute risk of any diabetes-related complication in the metformin group (29.8 events/1000 patient-years) versus diet alone (43.3 events/1000 patient-years), p=0.0023, and versus the combined sulfonylurea and insulin monotherapy

groups (40.1 events/1000 patient- years), p=0.0034;

- a significant reduction of the absolute risk of diabetes-related mortality: metformin 7.5 events/1000 patient-years, diet alone 12.7 events/1000 patient-years, p=0.017;

- a significant reduction of the absolute risk of overall mortality: metformin 13.5 events/1000 patient-years versus diet alone 20.6 events/1000 patient-years (p=0.011), and versus the combined sulfonylurea and insulin monotherapy groups 18.9 events/1000 patient-years (p=0.021);

- a significant reduction in the absolute risk of myocardial infarction: metformin 11 events/1000 patient-years, diet alone 18 events/1000 patients-years (p=0.01).

Benefit regarding clinical outcome has not been shown for metformin used as second-line therapy, in combination with a sulfonylurea.
In type 1 diabetes, the combination of metformin and insulin has been used in selected patients, but the clinical benefit of this combination has not been formally established

Paediatric population
Controlled clinical studies in a limited paediatric population aged 10-16 years treated for 1 year demonstrated a similar response in glycaemic control to that seen in adults.

5.2. Pharmacokinetics:

Absorption:
After an oral dose of metformin hydrochloride tablet, maximum plasma concentration (C_{max}) is reached in approximately 2.5 hours (t_{max}). Absolute bioavailability of a 500 mg or 850 mg metformin hydrochloride tablet is approximately 50-60% in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces was 20-30%.
After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption is non-linear.
At the recommended metformin doses and dosing schedules, steady state plasma concentrations are reached within 24 to 48 hours and are generally less than 1 microgram/ml. In controlled

clinical trials, maximum metformin plasma levels (C_{max}) did not exceed 5 microgram/ml, even at maximum doses.

Food decreases the extent and slightly delays the absorption of metformin. Following oral administration of a 850 mg tablet, a 40% lower plasma peak concentration, a 25% decrease in AUC (area under the curve) and a 35 minute prolongation of the time to peak plasma concentration were observed. The clinical relevance of these findings is unknown.

Distribution:

Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean volume of distribution (Vd) ranged between 63-276 l.

Metabolism:

Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.

Elimination:

Renal clearance of metformin is> 400 ml/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 hours.

When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin in plasma.

Paediatric population

Single dose study: After single doses of metformin hydrochloride 500 mg paediatric patients have shown similar pharmacokinetic profile to that observed in healthy adults.

Multiple dose study: Data are restricted to one study. After repeated doses of 500 mg twice daily for 7 days in paediatric patients the peak plasma concentration (Cmax) and systemic exposure (AUC0-t) were reduced by approximately 33% and 40%, respectively compared to diabetic adults who received repeated doses of 500 mg twice daily for 14 days. As the dose is individually titrated based on glycaemic control, this is of limited clinical relevance.

53. Preclinical Safety Data

Preclinical data reveal no special hazard for humans based on conventional studies on safety, pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and reproductive toxicity.

6. Pharmaceutical Particulars:

6.1. List of excipients:

S. No.	Ingredients	Functions
1.	Hypromellose BP	Polymer
2.	Povidone BP	Binder
3.	Pregelatinised Starch BP	Diluent
4.	Colloidal Anhydrous Silica BP/ Ph. Eur.	Glidant
5.	Magnesium Stearate Ph.Eur.	Lubricant
6.	Purified Water USP*	Granulating agent
7.	Isopropyl Alcohol BP*	Granulating agent

* Does not contribute to the tablet weight.

6.2. Incompatibilities*:*

Not Applicable

6.3. Shelf life:

36 months

6.4. Special precautions for storage*:*

Store in a dry place below 30°C.

6.5. Nature & contents of container:

3 x 10's blister (using Aluminum foil on one side and PVDC-coated PVC film on other side) packed in a carton along with a pack insert.

6.6 Manufacturer:

Neopharma, Abu Dhabi, UAE

Plot No. A1 89-95,

Industrial City of Abu Dhabi (ICAD),

Mussafah, Abu Dhabi, UAE

7. Marketing Authorization Holder:

Neopharma, Abu Dhabi, UAE

Plot No. A1 89-95,

Industrial City of Abu Dhabi (ICAD),

Mussafah, Abu Dhabi, UAE

8. Market authorization number

04932/06656/NMR/2018

9. Date of authorization

Jan 30, 2020

10. Date of Revision of Text:

10.02.2017