



20500

Ref. No: B2120500/20.01

# Dicard<sup>®</sup> (Tablets)

Sacubitril Valsartan trisodium salt hemipentahydrate  
Angiotensin II receptor blockers

DICARD<sup>®</sup> 50MG TABLETS (FILM COATED)  
DICARD<sup>®</sup> 100MG TABLETS (FILM COATED)  
DICARD<sup>®</sup> 200MG TABLETS (FILM COATED)

## PRESENTATION

**Dicard<sup>®</sup> 50 mg Film coated Tablet:** Light pink, circular, biconvex tablet plain on both the sides. Each film coated tablet contains: Sacubitril Valsartan and other excipients.

**Dicard<sup>®</sup> 100 mg Film coated Tablet:** Yellow, circular, biconvex tablet plain on both the sides. Each film coated tablet contains: Sacubitril Valsartan and other excipients.

**Dicard<sup>®</sup> 200 mg Film coated Tablet:** Pink, circular, biconvex tablet plain on both the sides. Each film coated tablet contains: Sacubitril Valsartan and other excipients.

## CLINICAL PHARMACOLOGY

Sacubitril/Valsartan exhibits the mechanism of action of an angiotensin receptor neprilysin inhibitor by simultaneously inhibiting neprilysin (neutral endopeptidase; NEP) via LBQ657, the active metabolite of the prodrug Sacubitril, and by blocking the angiotensin II type-1 (AT1) receptor via Valsartan. The complementary cardiovascular benefits of Sacubitril/Valsartan in heart failure patients are attributed to the enhancement of peptides that are degraded by neprilysin, such as natriuretic peptides (NP), by LBQ657 and the simultaneous inhibition of the effects of angiotensin II by Valsartan. NPs exert their effects by activating membrane-bound guanylyl cyclase-coupled receptors, resulting in increased concentrations of the second messenger cyclic guanosine monophosphate (cGMP), which could result in vasodilation, natriuresis and diuresis, increased glomerular filtration rate and renal blood flow, inhibition of renin and aldosterone release, reduction of sympathetic activity, and anti-hypertrophic and anti-fibrotic effects.

## PHARMACOKINETICS

### Absorption

Following oral administration, Sacubitril/Valsartan dissociates into Valsartan and the prodrug Sacubitril. Sacubitril is further metabolised to the active metabolite LBQ657. These reach peak plasma concentrations in 2 hours, 1 hour, and 2 hours, respectively. The oral absolute bioavailability of Sacubitril and Valsartan is estimated to be more than 60% and 23%, respectively. Following twice daily dosing of Sacubitril/Valsartan, steady-state levels of Sacubitril, LBQ657 and Valsartan are reached in three days. At steady state, Sacubitril and Valsartan do not accumulate significantly, while LBQ657 accumulates 1.6-fold. Administration with food has no clinically significant impact on the systemic exposures of Sacubitril, LBQ657 and Valsartan. Sacubitril/Valsartan can be administered with or without food.

### Distribution

Sacubitril, LBQ657 and Valsartan are highly bound to plasma proteins (94-97%). Based on the comparison of plasma and CSF exposures, LBQ657 crosses the blood brain barrier to a limited extent (0.28%). The average apparent volume of distribution of Valsartan and Sacubitril were 75 litres to 103 litres, respectively.

### Biotransformation

Sacubitril is readily converted to LBQ657 by carboxylesterases 1b and 1c; LBQ657 is not further metabolised to a significant extent. Valsartan is minimally metabolised, as only about 20% of the dose is recovered as metabolites. A hydroxyl metabolite of Valsartan has been identified in plasma at low concentrations (<10%).

### Elimination

Following oral administration, 52-68% of Sacubitril (primarily as LBQ657) and ~13% of Valsartan and its metabolites are excreted in urine; 37-48% of Sacubitril (primarily as LBQ657) and 86% of Valsartan and its metabolites are excreted in faeces.

## USES

Dicard is indicated in adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction.

## DOSAGE AND ADMINISTRATION

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The starting dose is 100 mg twice a day (one tablet in the morning and one tablet in the evening).

This dose can be doubled at 2-4 weeks to a usual recommended target dose of 200 mg twice a day (one tablet in the morning and one tablet in the evening) as tolerated by the patient.

Patients not currently taking an ACE inhibitor or an ARB or taking low doses of these medicinal products therefore can have starting dose of 50 mg twice daily.

Swallow the tablets with a glass of water. To be taken with or without food.

## CONTRA-INDICATIONS

- Hypersensitivity to the active substances or to any of the excipients.
- Concomitant use with ACE inhibitors.
- Known history of angioedema related to previous ACE inhibitor or ARB therapy.
- Hereditary or idiopathic angioedema.
- Concomitant use with aliskiren-containing medicinal products in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m<sup>2</sup>).
- Severe hepatic impairment, biliary cirrhosis and cholestasis.
- Second and third trimesters of pregnancy

# Dicard<sup>®</sup> (Tablets)

## ADVERSE EFFECTS

- Stop taking Dicard and seek immediate medical attention if you notice any swelling of the face, lips, tongue and/or throat, which may cause difficulties in breathing or swallowing. These may be signs of angioedema.

Other adverse effects that may be experienced are as follows:

Very common: Low blood pressure, High level of potassium in the blood, Decreased renal function

Common: Cough, Dizziness, Diarrhoea, Low level of red blood cells, Tiredness, Renal failure, Low level of potassium in the blood, Headache, Fainting, Weakness,

Feeling sick (nausea), Low blood pressure, Gastritis, Spinning sensation, Low level of sugar in the blood

Uncommon: Allergic reaction with rash and itching, Dizziness, Angioedema

## OVERDOSAGE

Limited data are available with regard to overdose in humans. A single dose of 583 mg Sacubitril/617 mg Valsartan and multiple doses of 437 mg Sacubitril/463 mg Valsartan (14 days) were studied in healthy volunteers and were well tolerated. Hypotension is the most likely symptom of overdose due to the blood pressure lowering effects of Sacubitril/Valsartan. Symptomatic treatment should be provided. The medicinal product is unlikely to be removed by haemodialysis due to high protein binding

## INTERACTIONS

### ACE inhibitors

The concomitant use of Sacubitril/Valsartan with ACE inhibitors is contraindicated, as the concomitant inhibition of neprilysin (NEP) and ACE may increase the risk of angioedema.

### Aliskiren

The concomitant use of Sacubitril/Valsartan with aliskiren-containing medicinal products is contraindicated in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m<sup>2</sup>).

### OATP1B1 and OATP1B3 substrates, e.g. statins

In vitro data indicate that Sacubitril inhibits OATP1B1 and OATP1B3 transporters. Dicard may therefore increase the systemic exposure of OATP1B1 and OATP1B3 substrates such as statins.

### PDE5 inhibitors including sildenafil

Addition of a single dose of Sildenafil to Sacubitril/Valsartan at steady state in patients with hypertension was associated with a significantly greater blood pressure reduction compared to administration of Sacubitril/Valsartan alone.

### Lithium

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors or angiotensin II receptor antagonists.

## SPECIAL WARNINGS AND PRECAUTIONS

Talk to your doctor, pharmacist or nurse before taking Dicard:

- If you are being treated with an angiotensin receptor blocker (ARB) or aliskiren.
- If you have ever had angioedema.
- If you have low blood pressure or are taking any other medicines that reduce your blood pressure (for example, a diuretic) or are suffering from vomiting or diarrhoea, especially if you are aged 65 years or more, or if you have kidney disease and low blood pressure.
- If you have severe kidney disease.
- If you are suffering from dehydration.
- If your kidney artery has narrowed.
- If you have liver disease.

## PREGNANCY AND LACTATION

The use of sacubitril /valsartan is not recommended during the first trimester of pregnancy and is contraindicated during the second and third trimesters of pregnancy. Because of the potential risk for adverse reactions in breast-fed newborns/infants, it is not recommended during breast-feeding. A decision should be made whether to abstain from breast-feeding or to discontinue Dicard while breast-feeding, taking into account the importance of sacubitril/valsartan to the mother.

## PHARMACEUTICAL PRECAUTIONS

Store in a dry place below 30°C. Protect from light. Keep all medicines out of the reach of children.

**LEGAL CATEGORY:** Prescription Only Medicine (POM)

®Regd. TM



**COSMOS**

Cosmos Limited,  
Rangwe Rd; Off Lunga Lungu Rd,  
Nairobi, Kenya