PIL OF DICARD 50MG TABLETS

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

Dicard 50 mg film coated Tablets

1.1 *Strength*

50 mg

1.2 *Pharmaceutical form*

Film coated Tablet

2. CLINICAL PARTICULARS

2.1 *Therapeutic indications*

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

2.2 *Posology and method of 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 50 mg or 100 mg twice a day (one tablet in the morning and one tablet in the evening).
The usual recommended target dose is 200 mg twice a day (one tablet in the morning and one tablet in the evening).
Swallow the tablets with a glass of water. To be taken with or without food.

3 Method of administration

Oral.

4 Contraindications

• 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^2).
• Severe hepatic impairment, biliary cirrhosis and cholestasis.
• Second and third trimesters of pregnancy

5 *Special warnings and precautions for use*

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.

6 ***Paediatric population***
NA

7 ***Interaction with other medicinal products and other forms of interaction***
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 m2).

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

8 ***Additional information on special populations***
NA
9 ***Paediatric population***
N/A

10 ***Fertility, pregnancy and lactation***
Pregnancy

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.

Valsartan

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however, a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with ARBs, similar risks may exist for this class of medicinal product. Unless continued ARB therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ARBs should be stopped immediately and, if appropriate, alternative therapy should be started. Exposure to ARBs therapy during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia).

Should exposure to ARBs have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken ARBs should be closely observed for hypotension.

Sacubitril

There are no data from the use of Sacubitril in pregnant women. Studies in animals have shown reproductive toxicity.

Sacubitril/Valsartan

There are no data from the use of Sacubitril/Valsartan in pregnant women. Animal studies with Sacubitril/Valsartan have shown reproductive toxicity.

Breast-feeding

It is not known whether Sacubitril/Valsartan is excreted in human milk. The components of Dicard, Sacubitril and Valsartan, were excreted in the milk of lactating rats. 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.

Fertility

There are no available data on the effect of Sacubitril/Valsartan on human fertility. No impairment of fertility was demonstrated in studies with it in male and female rats.

11 ***Effects on ability to drive and use machines***
Sacubitril/Valsartan has a minor influence on the ability to drive and use machines. When driving vehicles or operating machines it should be taken into account that occasionally dizziness or fatigue may occur.

12 ***Undesirable 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.
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

13 ***Overdose***
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.

14. PHARMACOLOGICAL PROPERTIES
14.1 ***Pharmacodynamic properties***
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.

14.2 Pharmacokinetic properties

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.

14.3 *Preclinical safety data*
Non-clinical data (including studies with Sacubitril and Valsartan components and/or Sacubitril/Valsartan) reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and fertility.

15. PHARMACEUTICAL PARTICULARS

15.1 *Shelf life*
2 Years

15.2 *Special precautions for storage*
Store in a dry place below 30˚C. Protect from light.

Keep all medicines out of the reach of children.

15.2 *Nature and contents of container*
Alu-Alu pack.

15.3 *Special precautions for disposal and other handling*
No special requirements.

16. MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE ADDRESSES

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