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

CORBIS D

1. Generic Name

Dapagliflozin 10 mg and Bisoprolol Fumarate 5 mg Tablets

2. Qualitative and quantitative Composition:

Each film coated tablet contains:

Dapagliflozin Propanediol USP eq. to

Dapagliflozin……10 mg

Bisoprolol Fumarate I.P……5 mg

Excipients …….q.s.

Colours : Lake Yellow Oxide of Iron and Titanium Dioxide IP

The excipients used are Microcrystalline Cellulose, Sodium Starch Glycolate, PVP K-30, Lactose, Crossprovidone, Colloidal Silicone Dioxide, Magnesium Stearate, Colorezy 17F520245 Yellow.

3. Dosage form and strength

Dosage form: Tablets

Strength: Dapagliflozin 10 mg and Bisoprolol Fumarate 5 mg

4. Clinical particulars

4.1 Therapeutic indication

It is indicated in patients with heart Failure with Reduced Ejection Fraction (HFrEF).

4.2 Posology and method of administration

The treatment of heart failure with Dapagliflozin & Bisoprolol FDC is initiated according to the following titration scheme, individual adaptation may be necessary depending on how well the patient tolerates each dose, i.e. the dose is to be increased only, if the previous dose is well tolerated.

- The recommended starting dose is Dapagliflozin 10 mg + Bisoprolol fumarate 5 mg once daily for 1-2 weeks and
- If well tolerated increase to Dapagliflozin 10 mg + Bisoprolol fumarate 10 mg once daily and continue long term.

Use in patients with mild to moderate renal insufficiency

This combination can be used in patients with mild to moderate renal insufficiency (eGFR ≥25 mL/min/1.73m2 BSA).:

4.3 Contraindications

This combination is contra-indicated in the case of,

- History of serious hypersensitivity reaction to dapagliflozin, bisoprolol or any of the excipients
- Severe bradycardia
- Second- or third-degree heart block
- Cardiogenic shock
- Decompensated cardiac failure
- Sick sinus syndrome (unless a permanent pacemaker is in place)
- Patients on dialysis.

4.4 Special warnings and precautions for use

General

Combination should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

Renal Impairment

There is limited experience with initiating treatment with combination especially dapagliflozin in patients with eGFR < 25 mL/min/1.73m2,and no experience with initiating treatment in patients with eGFR < 15 mL/min/1.73m2. Therefore, it is not recommended to initiate treatment with combination in patients with eGFR < 15 mL/min/1.73m2.

Hepatic impairment

There is limited experience in clinical studies in patients with hepatic impairment. Dapagliflozin exposure is increased in patients with severe hepatic impairment.

Use in patients at risk for volume depletion and/or hypotension

Due to its mechanism of action, dapagliflozin increases diuresis which may lead to the modest decrease in blood pressure observed in clinical studies. It may be more pronounced in patients with very high blood glucose concentrations. Caution should be exercised in patients for whom a dapagliflozin-induced drop in blood pressure could pose a risk, such as patients on anti-hypertensive therapy with a history of hypotension or elderly patients. In case of intercurrent conditions that may lead to volume depletion (e.g. gastrointestinal illness), careful monitoring of volume status (e.g. physical examination, blood pressure measurements, laboratory tests including haematocrit and electrolytes) is recommended. Temporary interruption of treatment with combination is recommended for patients who develop volume depletion until the depletion is corrected

Diabetic ketoacidosis

Rare cases of diabetic ketoacidosis (DKA), including life-threatening and fatal cases, have been reported in patients treated with sodiumglucose co-transporter 2 (SGLT2) inhibitors, including dapagliflozin. In several cases, the presentation of the condition was atypical with only moderately increased blood glucose values, below 14 mmol/L (250mg/dL). The risk of diabetic ketoacidosis must be considered in the event of non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue, or sleepiness. Patients should be assessed for ketoacidosis immediately if these symptoms occur, regardless of blood glucose level. In patients where DKA is suspected or diagnosed, combination treatment should be stopped immediately. Treatment should be interrupted in patients who are hospitalised for major surgical procedures or acute serious medical illnesses. Monitoring of ketones is recommended in these patients. Measurement of

blood ketone levels is preferred to urine. Treatment with combination may be restarted when the ketone values are normal, and the patient's condition has stabilized. Before initiating dapagliflozin, factors in the patient history that may predispose to ketoacidosis should be considered. SGLT2inhibitors should be used with caution in the patients who may be at higher risk of DKA.

Necrotising fasciitis of the perineum (Fournier's gangrene)

Post marketing cases of necrotising fasciitis of the perineum (also known as Fournier's gangrene) have been reported in female and male patients taking SGLT2 inhibitors. This is a rare but serious and potentially life-threatening event that requires urgent surgical intervention and antibiotic treatment. Patients should be advised to seek medical attention if they experience a combination of symptoms of pain, tenderness, erythema, or swelling in the genital or perineal area, with fever or malaise. Be aware that either urogenital infection or perineal abscess may precede necrotising fasciitis. If Fournier's gangrene is suspected, combination should be discontinued and prompt treatment (including antibiotics and surgical debridement) should be instituted.

Urinary tract infections:

Urinary glucose excretion may be associated with an increased risk of urinary tract infection; therefore, temporary interruption of combination should be considered when treating pyelonephritis or urosepsis.

Elderly (≥ 65 years):

Elderly patients may be at a greater risk for volume depletion and are more likely to be treated with diuretics. Elderly patients are more likely to have impaired renal function, and/or to be treated with anti- hypertensive medicinal products that may cause changes in renal function such as angiotensin- converting enzyme inhibitors (ACE-I) and angiotensin II type 1 receptor blockers (ARB). The same recommendations for renal function apply to elderly patients as to all patients.

Cardiac failure

Experience with combination especially dapagliflozin in NYHA class IV is limited.

Chronic kidney disease

There is no experience with combination especially dapagliflozin for the treatment of chronic kidney disease in patients without diabetes who do not have albuminuria.

Lower limb amputations

An increase in cases of lower limb amputation (primarily of the toe) has been observed in long- term, clinical studies in type 2 diabetes mellitus with SGLT2 inhibitors. It is unknown whether this constitutes a class effect. It is important to counsel patients with diabetes on routine preventative foot care.

Urine laboratory assessments

Due to its mechanism of action, patients taking dapagliflozin combination will test positive for glucose in their urine.

Bisoprolol fumarate

Bisoprolol must be used with caution in patients with:

- Hypertension or angina pectoris and accompanying heart failure.
- Diabetes mellitus showing large fluctuations in blood glucose values. Symptoms of hypoglycaemia can be masked.
- Strict fasting.
- Ongoing desensitisation therapy.
- AV block of first degree.
- Prinzmetal's angina; Cases of coronary vasospasm have been observed. Despite its high beta1 selectivity, angina attacks cannot be completely excluded when bisoprolol is administered to patients with Prinzmetal's angina.
- Peripheral arterial occlusive disease. Intensification of complaints may occur especially when starting therapy.

In patients undergoing the general anaesthesia beta-blockade reduces the incidence of arrhythmias and myocardial ischemia during induction and intubation, and the post-operative period. It is currently recommended that maintenance beta-blockade be continued perioperatively.The anaesthesist must be aware of beta-blockade because of the potential for interactions with other drugs, resulting in bradyarrhythmias, attenuation of the reflex tachycardia and the decreased reflex ability to compensate for blood loss. If it is thought necessary to withdraw beta-blocker therapy before surgery, this should be done gradually and completed about 48 hours before anaesthesia. Although cardioselective (beta1) beta-blockers may have less effect on lung function than nonselective beta-blockers, as with all beta-blockers, these should be avoided in patients with obstructive airways diseases, unless there are compelling clinical reasons for their use. Where such reasons exist, bisoprolol may be used with caution. In bronchial asthma or other chronic obstructive lung diseases, which may cause symptoms, bronchodilating therapy should be given concomitantly. Occasionally an increase of the airway resistance may occur in patients with asthma, therefore the dose of beta2- stimulants may have to be increased. As with other beta-blockers, bisoprolol may increase both the sensitivity towards allergens and the severity of anaphylactic reactions. Adrenaline treatment does not always give the expected therapeutic effect. Patients with psoriasis or with a history of psoriasis should only be given beta- blockers (e.g. bisoprolol) after carefully balancing the benefits against the risks. In patients with phaeochromocytoma bisoprolol must not be administered until after alpha-receptor blockade.

4.5 Drugs interactions

Dapagliflozin: Pharmacodynamic interactions

Diuretics: Dapagliflozin may add to the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension.

Insulin and insulin secretagogues: Insulin and insulin secretagogues, such as sulphonylureas, cause hypoglycaemia. Therefore, a lower dose of insulin or an insulin secretagogue may be required to reduce the risk of hypoglycaemia when used in combination with Dapagliflozin in patients with type 2 diabetes mellitus.

Pharmacokinetic interactions

The metabolism of dapagliflozin is primarily via glucuronide conjugation mediated by UDP glucuronosyltransferase 1A9(UGT1A9).In in vitro studies, dapagliflozin neither inhibited cytochrome P450 (CYP) 1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4,nor induced CYP1A2, CYP2B6 or CYP3A4. Therefore, dapagliflozin is not expected to alter the metabolic clearance of co- administered medicinal products that are

metabolised by these enzymes.Effect of other medicinal products on Dapagliflozin Interaction studies conducted in healthy subjects, using mainly a single-dose design, suggest that the pharmacokinetics of dapagliflozin are not altered by metformin, pioglitazone, sitagliptin, glimepiride, voglibose, hydrochlorothiazide, bumetanide, valsartan, or simvastatin.Following coadministration of dapagliflozin with rifampicin (an inducer of various active transporters and drug-metabolising enzymes) a 22% decrease in dapagliflozin systemic exposure (AUC) was observed, but with no clinically meaningful effect on 24-hour urinary glucose excretion. No dose adjustment is recommended. A clinically relevant effect with other inducers (e.g., carbamazepine, phenytoin, phenobarbital) is not expected. Following coadministration of dapagliflozin with mefenamic acid (an inhibitor of UGT1A9), a 55% increase in dapagliflozin systemic exposure was seen, but with no clinically meaningful effect on 24-hour urinary glucose excretion. No dose adjustment is recommended.

Effect of dapagliflozin on other medicinal products:

In interaction studies conducted in healthy subjects, using mainly a single-dose design, dapagliflozin did not alter the pharmacokinetics of metformin, pioglitazone, sitagliptin, glimepiride, hydrochlorothiazide, bumetanide, valsartan, digoxin (a P-GP substrate) or warfarin (S-warfarin, a CYP2C9 substrate), or the anticoagulatory effects of warfarin as measured by INR. Combination of a single dose of dapagliflozin 20 mg and simvastatin (a CYP3A4 substrate) resulted in a 19%increase in AUC of simvastatin and 31% increase in AUC of simvastatin acid. The increase in simvastatin and simvastatin acid exposures are not considered clinically relevant.

Interference with 1,5-anhydroglucitol (1,5-AG) assay

Monitoring glycaemic control with 1,5-AG assay is not recommended as measurements of 1,5- AG are unreliable in assessing glycaemic control in patients taking SGLT2 inhibitors. Use of alternative methods to monitor glycaemic control is advised.

Bisoprolol fumarate:

Combinations not recommended:

Calcium antagonists of the verapamil type and to a lesser extent of the diltiazem type: Negative influence on contractility and atrio-ventricular conduction. Intravenous administration of verapamil in patients on β-blocker treatment may lead to profound hypotension and atrio-ventricular block.

Centrally acting antihypertensive drugs such as clonidine and others:(e.g., methyldopa, moxonodine, rilmenidine)

Concomitant use of centrally acting antihypertensive drugs may worsen heart failure by a decrease in the central sympathetic tonus (reduction of heart rate and cardiac output, vasodilation). Abrupt withdrawal, particularly if prior to beta-blocker discontinuation, may increase risk of "rebound hypertension".

Combinations to be used with caution:

Calcium antagonists of the dihydropyridine type such as felodipine and amlodipine: Concomitant use may increase the risk of hypotension, and an increase in the risk of a further deterioration of the ventricular pump function in patients with heart failure cannot be excluded.

Class-III antiarrhythmic drugs (e.g., amiodarone):

Effect on atrio-ventricular conduction time may be potentiated. Topical beta-blockers (e.g., eye drops for glaucoma treatment) may add to the systemic effects of bisoprolol.

Parasympathomimetic drugs:

Concomitant use may increase atrio-ventricular conduction time and the risk of bradycardia.

Insulin and oral antidiabetic drugs:

Intensification of blood sugar lowering effect. Blockade of beta-adrenoreceptors may mask symptoms of hypoglycaemia (for example tachycardia).

Anaesthetic agents:

Attenuation of the reflex tachycardia and increase of the risk of hypotension

Digitalis glycosides:

Reduction of heart rate, increase of atrio-ventricular conduction time.

Non-steroidal anti-inflammatory drugs (NSAIDs):

NSAIDs may reduce the hypotensive effect of bisoprolol.

β-Sympathomimetic agents (e.g. isoprenaline, dobutamine):

Combination with bisoprolol may reduce the effect of both agents.

Sympathomimetics that activate both β- and α-adrenoceptors (e.g. noradrenaline, adrenaline):

Combination with bisoprolol may unmask the α-adrenoceptor-mediated vasoconstrictor effects of these agents leading to blood pressure increase and exacerbated intermittent claudication. Such interactions are considered to be more likely with nonselective β-blockers.

Concomitant use with antihypertensive agents as well as with other drugs with blood pressure lowering potential (e.g., tricyclic antidepressants, barbiturates, phenothiazines) may increase the risk of hypotension.

Combinations to be considered.

Mefloquine: Increased risk of bradycardia

Monoamine oxidase inhibitors (except MAO-B inhibitors):

Enhanced hypotensive effect of the beta-blockers but also risk for hypertensive crisis.

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

Dapagliflozin

Pregnancy

There are no data on the use of dapagliflozin in pregnant women. Studies in rats have shown toxicity to the developing kidney in the time period corresponding to the second and third trimesters of human pregnancy. Therefore, the use of dapagliflozin is not recommended during the second and third trimesters of pregnancy. When pregnancy is detected, treatment with this combination containing dapagliflozin should be discontinued.

Breast-feeding

It is unknown whether dapagliflozin and/or its metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of dapagliflozin/metabolites in milk, as well as pharmacologically mediated effects in nursing offspring. A risk to the newborns/infants cannot be excluded. Therefore, this combination containing dapagliflozin should not be used while breast-feeding.

Fertility

The effect of dapagliflozin on fertility in humans has not been studied. In male and female rats, dapagliflozin showed no effects on fertility at any dose tested.

Bisoprolol Fumarate:

Pregnancy and lactation Pregnancy

Bisoprolol has pharmacological effects that may cause harmful effects on pregnancy and/or the foetus/newborn. In general, f3-adrenoceptor blockers reduce placental perfusion, which has been associated with growth retardation, intrauterine death, abortion or early labour. Adverse effects (e.g. hypoglycaemia and bradycardia) may occur in the foetus and newborn infant. If treatment with f3-adrenoceptor blockers is necessary, f31-selective adrenoceptor blockers are preferable. Bisoprolol is not recommended during pregnancy unless clearly necessary. If treatment is considered necessary, monitoring of the uteroplacental blood flow and the foetal growth is recommended. In case of harmful effects on pregnancy or the foetus consideration of alternative treatment is recommended. The newborn infant must be closely monitored. Symptoms of hypoglycaemia and bradycardia are generally to be expected within the first 3 days.

Lactation

There are no data on the excretion of bisoprolol in human breast milk. Therefore, breastfeeding is not recommended during administration of bisoprolol.

4.7 Effects on ability to drive and use machines

Dapagliflozin and bisoprolol tablets have no or negligible influence on the ability to drive and use machines. However, patients should be made aware of the symptoms of hypotension and should be careful if driving or operating machinery, especially at the beginning of treatment. In a study with coronary heart disease patients, bisoprolol did not impair driving performance. However, due to individual variations in reactions to the drug, the ability to drive a vehicle or to operate machinery may be impaired. This is to be considered particularly at the start of treatment and upon change of medication as well as in conjunction with alcohol.

4.8 Undesirable effects

Dapagliflozin:

System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare
Infections and infestations		Vulvovaginitis, balanitis and related genital infections*, b,c Urinary tract infection*	Fungal infection**		Necrotising fasciitis of the perineum Founier)
Metabolism and nutrition disorders	Hypoglycaemia (when used with SU or insulin) b		Volume depletion b,e Thirst**	Diabetic ketoacidosis (when used in type 2 diabetes mellitus)	
Nervous system disorders		Dizziness			
Gastrointestinal disorders			Constipation** Dry mouth**		
Skin and subcutaneous tissue disorders		Rash			Angioedema
Musculoskeletal and connective tissue disorders		Back pain*			
Renal and urinary disorders		Dysuria *,f Polyuria	Nocturia**		
Reproductive system and breast disorders			Vulvovaginal pruritus** Pruritus genital**		
Investigations		Haematocrit increasedg Creatinine renal clearance decreased during initial treatment[b]	Blood creatinine increased during initial treatment**,b Blood urea increased** Weight decreased**		

c- Vulvovaginitis, balanitis and related genital infections includes, e.g. the predefined preferred terms: vulvovaginal mycotic infection, vaginal infection, balanitis, genital infection fungal, vulvovaginal candidiasis, vulvovaginitis, balanitis candida,genital candidiasis, genital infection, genital infection male, penile infection, vulvitis, vaginitis bacterial, vulval abscess.d- Urinary tract infection includes the following preferred terms, listed in order of frequency reported: urinary tract infection, cystitis, Escherichia urinary tract infection, genitourinary tract infection, pyelonephritis, trigonitis, urethritis, kidney infection and prostatitis.e- Volume depletion includes, e.g., the predefined preferred terms: dehydration,

hypovolaemia, hypotension.f- Polyuria includes the preferred terms: pollakiuria, polyuria, urine output increased.g- Mean changes from baseline in haematocrit were 2.30% for dapagliflozin 10 mg versus-0.33% for placebo. Haematocrit values >55% were reported in 1.3% of the subjects treated with dapagliflozin 10 mg versus 0.4% of placebo subjects.h- Mean percent change from baseline for dapagliflozin 10 mg versus placebo, respectively, was: total cholesterol 2.5%versus 0.0%; HDL cholesterol 6.0% versus 2.7%; LDL cholesterol 2.9% versus -1.0%; triglycerides –2.7% versus -0.7%.j- Adverse reaction was identified through postmarketing surveillance. Rash includes the following preferred terms, listed in order of frequency in clinical studies: rash, rash generalized, rash pruritic, rash macular, rash maculo-papular, rash pustular, rash vesicular, and rash erythematous. In active- and placebo-controlled clinical studies (dapagliflozin, N=5936, All control, N=3403), the frequency of rash was similar for dapagliflozin (1.4 %) and all control (1.4%), respectively.k- Reported in the cardiovascular outcomes study in patients with type 2 diabetes (DECLARE). Frequency is based on annual rate.*Reported in ? 2% of subjects and ? 1% more and at least 3 more subjects treated with dapagliflozin 10 mg compared to placebo.**Reported by the investigator as possibly related, probably related or related to study treatment and reported in ? 0.2%of subjects and ? 0.1% more and at least 3 more subjects treated with dapagliflozin 10 mg compared to placebo.

Bisoprolol fumarate:

Very common (≥1/10),

Common (≥1/100 to < 1/10),

Uncommon (≥1/1,000 to < 1/100),

Rare (≥1/10,000 to < 1/1,000),

Very rare (< 1/10,000),

Frequency not known (cannot be estimated from available data)

Investigations

Rare: increased triglycerides, increased liver enzymes (ALAT, ASAT).

Cardiac disorders

Uncommon: AV-conduction disturbances, worsening of pre-existing heart failure; bradycardia

Nervous system disorders

Common: dizziness*, headache*

Rare: syncope

Eye disorders

Rare: reduced tear flow (to be considered if the patient uses contact lenses)

Very rare: conjunctivitis

Ear and labyrinth disorders

Rare: hearing disorders

Respiratory, thoracic and mediastinal disorders

Uncommon: bronchospasm in patients with bronchial asthma or a history of obstructive airways disease

Rare: allergic rhinitis

Gastrointestinal disorders

Common: gastrointestinal complaints such as nausea, vomiting, diarrhoea, constipation

Skin and subcutaneous tissue disorders

Rare: hypersensitivity reactions (pruritus, flush, rash and angioedema)Very rare: alopecia. β-blockers may provoke or worsen psoriasis or induce psoriasis-like rash.

Musculoskeletal and connective tissue disorders

Uncommon: muscle weakness, muscle cramps.

Vascular disorders

Common: feeling of coldness or numbness in the extremities, hypotension

General disorders

Common: fatigue

Uncommon: asthenia Hepatobilary disorders

Rare: hepatitis

Reproductive system and breast disorders

Rare: erectile dysfunction

Psychiatric disorders

Uncommon: depression, sleep disorder

Rare: nightmare, hallucination

*These symptoms especially occur at the beginning of the therapy. They are generally mild and usually disappear within 1-2 weeks. An increased level of antinuclear antibodies (ANA) have been noticed, but the clinical relevance of this is not clear.

Reporting of adverse reactions

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: https://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

Dapagliflozin:

Dapagliflozin did not show any toxicity in healthy subjects at single oral doses up to 500 mg (50 times the maximum recommended human dose). These subjects had detectable glucose in the urine for a dose-related period of time (at least 5 days for the 500 mg dose), with no reports of dehydration, hypotension or electrolyte imbalance, and with no clinically meaningful effect on QTc interval. The incidence of hypoglycaemia was similar to placebo. In clinical studies where once-daily doses of up to 100 mg (10 times the maximum recommended human dose)

were administered for 2 weeks in healthy subjects and type 2 diabetes subjects, the incidence of hypoglycaemia was slightly higher than placebo and was not dose-related. Rates of adverse events including dehydration or hypotension were similar to placebo, and there were no clinically meaningful dose-related changes in laboratory parameters, including serum electrolytes and biomarkers of renal function. In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status. The removal of dapagliflozin by haemodialysis has not been studied.

Bisoprolol fumarate:

In general the most common signs expected with overdosage of a beta-blocker are bradycardia, hypotension, bronchospasm, acute cardiac insufficiency and hypoglycaemia. There is a wide interindividual variation in sensitivity to one single high dose of bisoprolol. If overdose occurs, bisoprolol treatment should be stopped and supportive and symptomatic treatment should be provided. Limited data suggest that bisoprolol is hardly dialysable. Based on the expected pharmacologic actions and recommendations for other beta-blockers, the following general measures should be considered when clinically warranted.

Bradycardia: Administer intravenous atropine. If the response is inadequate, isoprenaline or another agent with positive chronotropic properties may be given cautiously. Under some circumstances, transvenous pacemaker insertion may be necessary.

Hypotension: Intravenous fluids and vasopressors should be administered. Intravenous glucagon may be useful.

AV block (second or third degree): Patients should be carefully monitored and treated with isoprenaline infusion or transvenous cardiac pacemaker insertion.

Acute worsening of heart failure: Administer i.v. diuretics, inotropic agents, vasodilating agents.

Bronchospasm: Administer bronchodilatorHypoglycaemia: Administer i.v. glucose therapy such as isoprenaline, beta2-sympathomimetic drugs and/or aminophylline.

5 Pharmacological properties

5.1 Mechanism of Action

Dapagliflozin:

Dapagliflozin is a highly potent (Ki : 0.55 nM), selective and reversible inhibitor of SGLT2. Inhibition of SGLT2 by Dapagliflozin reduces sodium and glucose reabsorption. Reduction in sodium and glucose reabsorption leads to and osmotic diuresis and urinary excretion of glucose. Dapagliflozin therefore increases the delivery of sodium to the distal tubule which increases tubuloglomerular feedback and reduces intraglomerular pressure. This combined with osmotic diuresis leads to a reduction in volume overload, reduced blood pressure, and lower preload and afterload, which may have beneficial effects on cardiac remodelling and preserve renal function. Other effects include an increase in haematocrit and reduction in body weight. The cardiac and renal benefits of dapagliflozin are not solely dependent on the blood glucose-lowering effect and not limited to patients with diabetes as demonstrated in the DAPA-HF and DAPA-CKD studies

Bisoprolol fumarate:

Bisoprolol is a highly beta1-selective-adrenoceptor blocking agent, lacking intrinsic stimulating and relevant membrane stabilising activity. It only shows low affinity to the beta2-receptor of the smooth muscles of bronchi and vessels as well as to the beta2-receptors concerned with metabolic regulation. Therefore, bisoprolol is generally not to be expected to influence the airway resistance and beta2- mediated metabolic effects. Its beta1-selectivity extends beyond the therapeutic dose range. Bisoprolol has a negative inotropic and chronotropic effect. Bisoprolol reaches its maximal effect 3-4 hours after oral administration. The maximal antihypertensive effect of bisoprolol is generally reached after 2 weeks. In acute administration, bisoprolol reduces the heart rate and stroke volume, thus reducing cardiac output. In chronic administration the initially elevated peripheral resistance decreases.

5.2 Pharmacodynamic properties

Dapagliflozin:

This urinary glucose excretion with dapagliflozin also results in osmotic diuresis and increases in urinary volume in subjects with type 2 diabetes mellitus. Urinary volume increases in subjects with type 2 diabetes mellitus treated with dapagliflozin 10 mg were sustained at 12 weeks and amounted to approximately 375 mL/day. The increase in urinary volume was associated with a small and transient increase in urinary sodium excretion that was not associated with changes in serum sodium concentrations. Urinary uric acid excretion was also increased transiently (for 3-7 days) and accompanied by a sustained reduction in serum uric acid concentration. At 24 weeks, reductions in serum uric acid concentrations ranged from -48.3 to -18.3micromoles/L (-0.87 to -0.33 mg/dL).

Clinical efficacy and safety in heart failure

Dapagliflozin And Prevention of Adverse outcomes in Heart Failure (DAPA-HF) was an international, multicentre, randomised, double-blind, placebo-controlled study in patients with heart failure (New York Heart Association [NYHA]functional class II-IV) with reduced ejection fraction (left ventricular ejection fraction [LVEF] ≤ 40%). Of 4,744 patients, 2,373 were randomised to dapagliflozin 10 mg and 2,371 to placebo and followed for a median of 18 months. The treatment benefit of dapagliflozin was observed in heart failure patients both with type 2 diabetes mellitus and without diabetes. Dapagliflozin reduced the primary composite endpoint of incidence of cardiovascular death and worsening heart failure with a HR of 0.75 (95% CI 0.63, 0.90) in patients with diabetes and 0.73 (95% CI 0.60, 0.88) in patients without diabetes.

Bisoprolol fumarate:

Clinical efficacy and safetyIn total 2647 patients were included in the CIBIS II trial. 83% (n = 2202) were in NYHA class III and 17% (n = 445) were in NYHA class IV. They had stable symptomatic systolic heart failure (ejection fraction ≤35%, based on echocardiography). Total mortality was reduced from 17.3% to 11.8% (relative reduction 34%). A decrease in sudden death (3.6% vs 6.3%, relative reduction 44%) and a reduced number of heart failure episodes requiring hospital admission (12% vs 17.6%, relative reduction 36%) was observed. Finally,a significant improvement of the functional status according to NYHA classification has been shown. During the initiation and titration of bisoprolol hospital admission due to bradycardia (0.53%), hypotension (0.23%), and acute decompensation (4.97%) were observed, but they were not more frequent than in the placebo group (0%, 0.3% and 6.74%). The numbers of fatal and disabling strokes during the total study period were 20 in the bisoprolol group and 15 in the placebo group.The CIBIS III trial investigated 1010 patients aged ≥65 years with

mild to moderate chronic heart failure (CHF; NYHA class II or III) and left ventricular ejection fraction ≤35%, who had not been treated previously with ACE inhibitors, beta-blocking agents, or angiotensin receptor blockers. Patients were treated with a combination of bisoprolol and enalapril for 6 to 24 months after an initial 6 months of treatment with either bisoprolol or enalapril.There was a trend toward a higher frequency of chronic heart failure worsening when bisoprolol was used as the initial 6-month treatment. Non-inferiority of bisoprolol-first versus enalapril-first treatment was not proven in the per-protocol analysis, although the two strategies for initiation of CHF treatment showed a similar rate of the primary combined endpoint death and hospitalization at the study end (32.4% in the bisoprolol-first group vs. 33.1 % in the enalapril-first group, per- protocol population). The study shows that bisoprolol can also be used in elderly chronic heart failure patients with mild to moderate disease.

Antianginal mechanism: Bisoprolol by inhibiting the cardiac beta receptors inhibits the response given to sympathetic activation. That results in a decrease in heart rate and contractility this way decreasing the oxygen demand of the cardiac muscle.In acute administration in patients with coronary heart disease without chronic heart failure bisoprolol reduces the heart rate and stroke volume and thus the cardiac output and oxygen consumption. In chronic administration, the initially elevated peripheral resistance decreases.

5.3 Pharmacokinetic properties

Dapagliflozin:

Absorption

Dapagliflozin was rapidly and well absorbed after oral administration. Maximum dapagliflozin plasma concentrations (Cmax) were usually attained within 2 hours after administration in the fasted state. Geometric mean steady-state dapagliflozin C max and AUC values following once daily 10 mg doses of dapagliflozin were 158 ng/mL and 628 ngh/mL, respectively. The absolute oral bioavailability of Dapagliflozin following the administration of a 10 mg dose is 78%. Administration with a high-fat meal decreased dapagliflozin Cmax by up to 50% and prolonged Tmax by approximately 1-hour but did not alter AUC as compared with the fasted state. These changes are not considered to be clinically meaningful. Hence, dapagliflozin can be administered with or without food.

Distribution

Dapagliflozin is approximately 91% protein bound. Protein binding was not altered in various disease states (e.g., renal, or hepatic impairment). The mean steady-state volume of distribution of dapagliflozin was 118 litres.

Metabolism

Dapagliflozin is extensively metabolised, primarily to yield dapagliflozin 3-O-glucuronide, which is an inactive metabolite. Dapagliflozin 3-O-glucuronide or other metabolites do not contribute to the glucose-lowering effects. The formation of dapagliflozin 3-O-glucuronide is mediated by UGT1A9, an enzyme in the liver and kidney, and CYP-mediated metabolism was a minor clearance pathway in humans.

Excretion

The mean plasma terminal half-life (t1/2) for dapagliflozin was 12.9 hours following a single oral dose of dapagliflozin 10 mg to healthy subjects. The mean total systemic clearance of

dapagliflozin administered intravenously was 207 mL/min. Dapagliflozin and related metabolites are primarily eliminated via urinary excretion with less than 2% as unchanged dapagliflozin. After administration of a 50 mg [14C]-dapagliflozin dose, 96% was recovered, 75% in urine and 21% in faeces. In faeces, approximately 15% of the dose was excreted as parent drug.

Linearity

Dapagliflozin exposure increased proportional to the increment in dapagliflozin dose over the range of 0.1 to 500 mg and its pharmacokinetics did not change with time upon repeated daily dosing for up to 24 weeks.

Bisoprolol fumarate:

Absorption

Bisoprolol is absorbed almost completely from the gastrointestinal tract. Together with the very small first pass effect in the liver, this results in a high bioavailability of approximately 90%. The plasma protein binding of bisoprolol is about 30%. The distribution volume is 3.5 l/kg. The total clearance is approximately 15 l/h.

Distribution

The plasma elimination half-life (10-12 hours) provides 24 hours efficacy following a once daily dosage.

Biotransformation and Elimination

Bisoprolol is excreted from the body by two routes. 50% is metabolised by the liver to inactive metabolites which are then excreted by the kidneys. The remaining 50% is excreted by the kidneys in an unmetabolized form. Since the elimination takes place in the kidneys and the liver to the same extent a dosage adjustment is not required for patients with impaired liver function or renal insufficiency.

Special population

In patients with chronic heart failure (NYHA stage III), the plasma levels of bisoprolol are higher and the half-life is prolonged compared to healthy volunteers. Maximum plasma concentration at steady state is 64±21 ng/ml at a daily dose of 10 mg and the half-life is 17±5 hours.

6 Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Dapagliflozin:

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and fertility. Dapagliflozin did not induce tumors in either mice or rats at any of the doses evaluated in two-year carcinogenicity studies.Reproductive and developmental toxicity: Direct administration of dapagliflozin to weanling juvenile rats and indirect exposure during late pregnancy (time periods corresponding to the second and third trimesters of pregnancy with respect to human renal maturation) and lactationare each associated with increased incidence and/or severity of renal pelvic and tubular dilatations in progeny.In a juvenile toxicity study, when dapagliflozin was dosed directly to young rats from postnatal day 21 until postnatal day90, renal pelvic and

tubular dilatations were reported at all dose levels; pup exposures at the lowest dose tested were ≥15 times the maximum recommended human dose. These findings were associated with dose-related increases in kidney weight and macroscopic kidney enlargement observed at all doses. The renal pelvic and tubular dilatations observed in juvenile animals did not fully reverse within the approximate 1-month recovery period.In a separate study of pre-and postnatal development, maternal rats were dosed from gestation day 6 through postnatal day 21, and pups were indirectly exposed in utero and throughout lactation. (A satellite study was conducted to assess dapagliflozin exposures in milk and pups.) Increased incidence or severity of renal pelvic dilatation was observed in adult offspring of treated dams, although only at the highest dose tested (associated maternal and pup dapagliflozin exposures were 1,415 times and 137 times, respectively, the human values at the maximum recommended human dose).

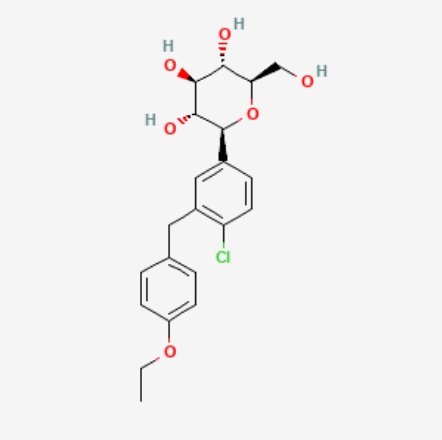
Bisoprolol fumarate:

Carcinogenesis, Mutagenesis, Impairment of Fertility

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeateddose toxicity, genotoxicity or carcinogenicity. Like other beta-blocking agents, bisoprolol caused maternal (decreasedfood intake and decreased body weight) and embryo/fetal toxicity (increased incidence of resorptions, reduced birthweight of the offspring, retarded physical development) at high doses but was not teratogenic.

7 Description

Dapagliflozin is (2S,3R,4R,5S,6R)-2-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-6-(hydroxymethyl) oxane-3,4,5-triol. The empiric formula of $C_{21}H_{25}ClO_6$ and its molecular weight is 408.9 g/mol. Its structural formula is:



Bisoprolol Fumarate is (E)-but-2-enedioic acid;1-(propan-2-ylamino)-3-[4-(2-propan-2-yloxyethoxymethyl)phenoxy]propan-2-ol. The empiric formula of $C_{40}H_{66}N_2O_{12}$ and its molecular weight is 767.0 g/mol. Its structural formula is:

Dapagliflozin and Bisoprolol Fumarate tablets is Yellow coloured, round shaped, film coated tablets, having plain surface both sides. The excipients used are Microcrystalline Cellulose, Sodium Starch Glycolate, PVP K-30, Lactose, Crossprovidone, Colloidal Silicone Dioxide, Magnesium Stearate, Colorezy 17F520245 Yellow.

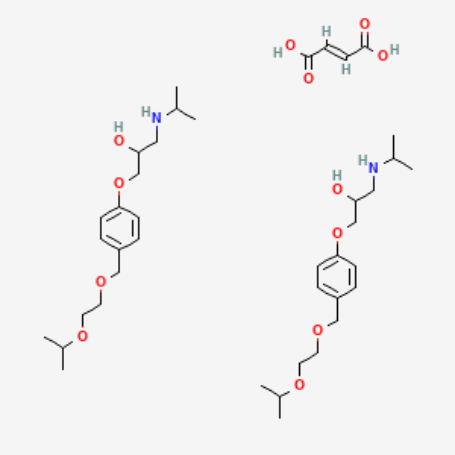
8 Pharmaceutical particulars

8.1 Incompatibilities

Not applicable

8.2 Shelf-life

Do not use later than date of expiry.



8.3 Packaging information

CORBIS D are packed in 10 Tablets.

8.4 Storage and handing instructions

Store at a temperature not exceeding 30°C.

9 Patient Counselling Information

Ask the patients to inform the treating physicians in case of any of the below:

- Have any allergies
- Have kidney or liver problems
- Are pregnant or plan to become pregnant
- Are breastfeeding or plan to breastfeed
- Have any serious illness
- Are taking any medicines (prescription, over-the-counter, vitamins, or herbal products)

10 Details of manufacturer

Manufactured by:

Eris Lifesciences Limited,

Amingaon, North Guwahati, Dist.

Kamrup-781031 (Assam).

11 Details of permission or licence number with date

Mfg Lic No. 377/DR/mfg/2014 issued on 21.08.2024

12. Date of revision

NA

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TORRENT PHARMACEUTICALS LTD.

IN/CORBIS D/Sep-24/01/PI