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SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

DYNARB 150 mg tablets

DYNARB 300 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DYNARB 150 mg: Each tablet contains 150 mg irbesartan.

DYNARB 300 mg: Each tablet contains 300 mg irbesartan.

DYNARB contains sugar (lactose monohydrate). Each 150 mg tablet contains 30,8 mg and each 300 mg tablet contains 61,5 mg of lactose monohydrate.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Tablet.

DYNARB 150 mg: White, cylindrical, biconvex, scored tablets with a diameter of 11 mm.

DYNARB 30 mg: White, oblong, biconvex, scored tablets with dimensions of 18,3 mm x 8,2 mm.

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4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DYNARB is indicated for:

- the treatment of essential hypertension. It may be used either alone or in combination with other antihypertensive medicines
- the treatment of diabetic nephropathy associated with elevated serum creatinine and proteinuria (> 300 mg/day) in patients with type 2 diabetes and hypertension.

4.2 Posology and method of administration

Posology

Adults

The usual recommended initial and maintenance dose is 150 mg once daily. In patients insufficiently controlled with 150 mg once daily, the dose of DYNARB can be increased to 300 mg or other anti-hypertensive medicines may be added.

Special populations

In patients with hypertension and type 2 diabetic renal disease

The preferred maintenance dose is 300 mg of DYNARB once daily.

Elderly patients and patients with renal or hepatic impairment

Generally, no dosage reduction is necessary in the elderly or in patients with mild to moderately impaired renal function or impaired hepatic function (mild to moderate degree).

Patients with intravascular volume depletion

A lower initial dose of DYNARB is recommended (see section 4.4 Hypotension-volume-depleted patients).

Paediatric population

The safety and efficacy of DYNARB in children aged 0 to 18 has not been established. No recommendation on posology can be made.

Method of administration

For oral use.

DYNARB can be taken with or without foo.

Missed dose

Doctors should advise patients who forget to take DYNARB to take a dose as soon as possible and then continue with the normal dose. Patients should not take a double dose to compensate for the missed dose.

4.3 Contraindications

Contraindications to be presented in bullet format where relevant

- hypersensitivity to irbesartan or to any of the ingredients of DYNARB (see section 6.1)
- a history of angioedema related to previous therapy with ACE inhibitors or angiotensin receptor blockers (ARBs). These patients must never again be given these medicines
- hereditary or idiopathic angioedema
- hypertrophic obstructive cardiomyopathy (HOCM)

- severe renal function impairment (creatinine clearance less than 30 mL/min)
- moderate to severe renal impairment in patients concomitantly using fluoroquinolones
- severe hepatic impairment
- bilateral renal artery stenosis
- renal artery stenosis in patients with a single kidney, or a transplanted kidney
- aortic stenosis
- concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride (see section 4.5)
- porphyria
- lithium therapy: Concomitant administration with DYNARB may lead to toxic blood concentrations of lithium (see section 4.5)
- pregnancy and lactation (see section 4.6)
- the concomitant use of DYNARB with renin inhibitors such as aliskiren- containing products is contraindicated (see sections 4.4 and 4.5).

Safety and efficacy in paediatric patients has not been established.

4.4 Special warnings and precautions for use

Should a woman become pregnant while receiving DYNARB, treatment must be stopped promptly and switched to a different class of antihypertensive medicine (see sections 4.3 and 4.6).

Hypotension-volume-depleted patients

DYNARB has been associated with hypotension in hypertensive patients without other co-morbid conditions. Symptomatic hypotension may be expected to occur in sodium/volume-depleted patients such as those treated with diuretics and/or salt restriction, or on haemodialysis. Volume and/or sodium-depletion should be corrected before initiating therapy with DYNARB or a lower starting dose (DYNARB 75 mg) should be considered.

Intravascular volume depletion

Symptomatic hypotension, especially after the first dose, may occur in patients who are volume and/or sodium depleted by vigorous diuretic therapy, dietary salt restriction, excessive perspiration, dialysis and diarrhoea or vomiting. Such conditions should be corrected before the administration of DYNARB or a lower starting dose should be considered (see section 4.2).

Renal impairment and kidney transplantation

When DYNARB is used in patients with impaired renal function, a periodic monitoring of potassium and creatinine serum levels is recommended (see section 4.5). As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. There is no experience regarding the administration of DYNARB in patients with a recent kidney transplantation.

Renovascular hypertension

There is an increased risk of severe hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with medicines that affect the renin-angiotensin-aldosterone system. A similar effect should be

anticipated with angiotensin-II receptor antagonists such as DYNARB (see section 4.3).

The use of DYNARB in patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney is contraindicated (see section 4.3).

Heart failure

In patients with heart failure, with or without renal impairment, there is a risk of acute hypotension, uraemia, oliguria and (often acute) renal failure and/or death.

Hypertensive patients with type 1 and 2 diabetes

DYNARB should be used with caution in diabetics with reduced awareness of hypoglycaemia.

Hypertensive patients with type 2 diabetes and renal disease

The effects of irbesartan both on renal and cardiovascular events were not uniform across all subgroups, in an analysis carried out in the study with patients with advanced renal disease. In particular, they appeared less favourable in women and non-white subjects.

Fluoroquinolones and ARBs

Concomitant use of fluoroquinolones and ARBs may precipitate acute kidney injury in patients especially those with moderate to severe renal impairment and elderly patients (see section 4.3). Renal function should be assessed before initiating treatment and monitored during treatment with fluoroquinolones or ARBs whether used separately and/or concomitantly.

Lithium

The combination of lithium and DYNARB is contraindicated (see sections 4.3 and 4.5).

Hyperkalaemia

Hyperkalaemia may occur during the treatment with DYNARB, especially in the presence of renal impairment, overt proteinuria due to diabetic renal disease, and/or heart failure. Close monitoring of serum potassium in patients at risk is recommended (see section 4.5).

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

There is evidence that the concomitant use of ACE-Inhibitors, angiotensin II receptor blockers (ARBs) or aliskiren may increase the risk of hypotension, hyperkalaemia and decreases renal function (including acute renal failure). Dual blockade of RAAS through the combined use of DYNARB and renin inhibitors such as aliskiren is therefore contraindicated (see section 4.3).
DYNARB should not be used concomitantly with renin inhibitors such as aliskiren (see section 4.3).
ACE-inhibitors and angiotensin II receptor blockers should
not be used concomitantly in patients with diabetic nephropathy.

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy

Special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

Primary aldosteronism

Patients with primary aldosteronism may not respond to antihypertensive medicines acting through inhibition of the renin-angiotensin system. Therefore, the use of DYNARB is not recommended.

Coronary heart disease and cerebrovascular disease

Excessive blood pressure decrease in patients with ischaemic cardiomyopathy or ischaemic cardiovascular disease could result in a myocardial infarction or stroke.

Hypoglycaemia

DYNARB may induce hypoglycaemia, particularly in diabetic patients. In patients treated with insulin or antidiabetics an appropriate blood glucose monitoring should be considered; a dose adjustment of insulin or antidiabetics may be required when indicated (see section 4.5).

Ethnic groups

DYNARB may be less effective in lowering blood pressure in black patients than in nonblack patients, possibly because of higher prevalence of low-renin states in the black hypertensive population.

Use in elderly

There is no reported age-related difference in the efficacy or safety profile of DYNARB.

Information on excipients of DYNARB

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Paediatric population

Irbesartan has been studied in paediatric populations aged 6 to 16 years old but the current data are insufficient to support an extension of the use in children until further data become available

(see section 4.3).

4.5 Interaction with other medicines and other forms of interaction

Combinations containing any of the following medicines, may interact with DYNARB

- ***fluoroquinolones:*** concomitant use of ARBs and fluoroquinolones may precipitate acute kidney injury. The mechanism of the possible interaction between the different classes of medicines, over and above different mechanisms of kidney damage, is unknown (see section 4.3)
- ***dual blockade of the RAAS with ARBs, ACE inhibitors, or aliskiren:*** Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE inhibitors, angiotensin II receptor blockers or renin inhibitors such as aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting medicine (see sections 4.3 and 4.4)
- ***diuretics and other hypertensive medicines:*** may increase the hypotensive effects of DYNARB. However, DYNARB may be administered with other antihypertensive medicines, such as beta-blockers, long-acting calcium channel blockers, and thiazide diuretics. Prior treatment with high dose diuretics may result in volume depletion and a risk of hypotension when initiating therapy with DYNARB (see section 4.4)
- ***lithium:*** serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with DYNARB, therefore, this combination is contraindicated (see section 4.3)
- ***potassium-sparing diuretics, potassium supplements:*** concomitant use of DYNARB and potassium-sparing diuretics, potassium supplements or salt substitutes containing potassium

may, or other medicines that may increase serum potassium levels (such as heparin) may lead to increases in serum potassium, and is therefore not recommended (see section 4.4). The use of potassium-sparing diuretics together with DYNARB is contraindicated (see section 4.3)

- ***non-steroidal anti-inflammatory medicines (NSAIDs):*** when angiotensin II antagonists, such as DYNARB, are administered simultaneously with NSAIDs (i.e. selective COX-2 inhibitors, aspirin (> 3 g/day) and non- selective NSAIDs), attenuation of the antihypertensive effect may occur. Concomitant use of DYNARB and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. These effects may be reversible. The combination should be administered with caution, especially in the elderly, volume-depleted (including those on diuretic therapy) or with compromised renal function. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter
- ***repaglinide:*** irbesartan has the potential to inhibit OATP1B1. In a clinical study, it was reported that irbesartan increased the C_{max} and AUC of repaglinide (substrate of OATP1B1) by 1.8-fold and 1.3-fold, respectively, when administered 1 hour before repaglinide. In another study, no relevant pharmacokinetic interaction was reported, when the two medicines were co-administered. Therefore, dose adjustment of antidiabetic treatment such as repaglinide may be required (see section 4.4)

Additional interaction information:

- the pharmacokinetics of DYNARB are not affected by the co-administration with nifedipine, warfarin or hydrochlorothiazide

- the pharmacokinetics of digoxin or simvastatin are not altered by co-administration of DYNARB
- the effects of CYP2C9 inducers such as rifampicin on the pharmacokinetic of irbesartan have not been evaluated.

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and lactation has not been established (see section 4.3).

Women of childbearing potential

Women of childbearing age should ensure effective contraception.

Pregnancy

When pregnancy is planned or confirmed DYNARB should be discontinued.

Medicines affecting the renin-angiotensin system, such as DYNARB can cause embryonal toxicity, foetal and neonatal morbidity and mortality when administered to pregnant women.

DYNARB passes through the placenta and can be presumed to cause disturbance in foetal blood pressure regulatory mechanisms. The use of DYNARB during the first trimester of pregnancy has been associated with an increased risk of birth defects, in particular, to the cardiovascular and the central nervous systems. Oligohydramnios as well as hypotension, oliguria and anuria in new-borns, have been reported after administration of DYNARB in the second and third trimester. Cases of defective skull ossification have been observed.

Prematurity and low birth mass can occur (see sections 4.3 and 4.4).

Patients planning pregnancy should be changed to alternative antihypertensive treatments, which have an established safety profile for use in pregnancy.

Breastfeeding

It is not known whether irbesartan is distributed into breast milk. However, because of potential for adverse effects in the breastfeeding infant, DYNARB should not be administered to breastfeeding mothers.

Available pharmacodynamic/toxicological data in rats have shown excretion of irbesartan or its metabolites in milk.

Fertility

Irbesartan had no effect upon fertility of treated rats and their offspring up to the dose levels inducing the first signs of parental toxicity.

4.7 Effects on ability to drive and use machines

Based on its pharmacodynamic properties, irbesartan is unlikely to affect the ability to drive and use machines, however, DYNARB can cause side effects such as dizziness and fatigue. Patients should be cautioned about engaging in activities requiring rapid and precise responses such as driving a vehicle or operating machinery until they know how DYNARB affects them.

4.8 Undesirable effects

Tabulated list of adverse effects

System Organ Class	Frequency	Side effects
Blood and lymphatic system disorders	Less frequent Frequency unknown	Neutropenia, hyperkalaemia Anaemia, thrombocytopenia
Immune system disorders	Less frequent	Hypersensitivity reactions** (e.g. urticaria, angioedema, rash, anaphylactic shock)
Endocrine disorders	Less frequent	Pancreatitis

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Metabolism and nutrition disorders	Frequency unknown	Hyperkalaemia* and **, hypoglycaemia**
Nervous system disorders	Frequent Frequency unknown	Dizziness, headache**, orthostatic dizziness* Migraine
Ear and labyrinth disorders	Frequent Frequency unknown	Vertigo** Tinnitus
Cardiac disorders	Less frequent	Tachycardia, hypotension
Vascular disorders	Frequent Less frequent	Orthostatic hypotension* Vasculitis, flushing
Respiratory, thoracic and mediastinal disorders	Less frequent	Cough, respiratory tract infection
Gastrointestinal disorders	Frequent Less frequent	Nausea, vomiting Diarrhoea, dyspepsia/heartburn, dysgeusia, gastrointestinal disturbances
Hepatobiliary disorders	Less frequent	Abnormal liver function**, cholestatic jaundice**, hepatitis**
Skin and subcutaneous tissue disorders	Less frequent	Leukocytoclastic vasculitis, rash, urticaria, pruritus, Henoch-Schonlein purpura
Musculoskeletal, connective tissue and bone disorders	Frequent Frequency unknown	Musculoskeletal pain* Arthralgia**, myalgia** (in some cases associated with increased plasma creatine kinase levels), muscle cramps, rhabdomyolysis, asthenia**
Renal and urinary disorders	Less frequent	Impaired renal function, renal failure in patients at risk**

Pregnancy, puerperium and perinatal conditions	Frequency unknown	Teratogenic potential
Reproductive system and breast disorders	Less frequent	Sexual dysfunction
General disorders and administrative site conditions	Frequent Less frequent Frequency unknown	Fatigue Chest pain, back pain Oedema
Investigations	Frequent	Decrease in haemoglobin in patients with advanced diabetic renal disease, increased plasma creatine kinase

* Adverse effects reported in diabetic hypertensive patients.

** Post marketing

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.
An email can be sent directly to the company, pharmacovigilance@pharmadynamics.co.za, to ensure safety of the product.

4.9 Overdose

Signs and symptoms

Experience in adults exposed to doses of up to 900 mg/day for 8 weeks revealed no toxicity.

The most common signs and symptoms observed are bradycardia, hypotension or tachycardia.

Management of overdose

No specific information is available on the treatment of overdosage with irbesartan.

The patient should be closely monitored and treatment should be symptomatic and supportive. Suggested measures include induction of emesis. Activated charcoal may be useful in the treatment of overdose. DYNARB is not removed from the body by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin-II antagonists, plain

ATC code: C09CA04

Pharmacological classification: A.7.1.3 Other hypotensives.

Mechanism of action

Irbesartan is a non-peptide angiotensin II antagonist that selectively blocks the binding of angiotensin II to the AT1 receptor. Angiotensin II is an important component of the renin-angiotensin system [conversion of angiotensin I by angiotensin-converting enzyme (ACE) to angiotensin II] and is involved in the pathophysiology of hypertension and in sodium homeostasis. Angiotensin II stimulates the adrenal cortex to synthesise and secrete aldosterone, which decreases the excretion of sodium and increases the excretion of potassium.

Irbesartan blocks the vasoconstrictor and aldosterone secreting effects of angiotensin II by selective antagonism of the angiotensin II (AT1 subtype) receptors localised on vascular smooth muscle cells and in the adrenal cortex. By preventing these effects of angiotensin II,

irbesartan relaxes smooth muscles and thereby promotes vasodilation, increases renal salt and water excretion, reduces plasma volume, and decreases cellular hypertrophy.
Irbesartan has no notable effects on serum triglycerides, cholesterol or glucose concentrations. There is no effect on serum uric acid or urinary uric acid excretion.

5.2 Pharmacokinetic properties

Absorption

After oral administration, irbesartan is well absorbed. The average absolute bioavailability ranges from 60 % to 80 %. Food does not affect the bioavailability. Peak plasma levels are obtained approximately 1,5 to 2 hours after oral administration and the plasma half-life ranges from 11 to 15 hours.

Distribution

Irbesartan is approximately 96 % protein-bound in the plasma, and has negligible binding to circular components of the blood. The volume of distribution is 53 to 93 litres. In plasma, unchanged irbesartan accounts for 80 – 85 % of the circulating radioactivity following oral or intravenous administration of ^{14}C irbesartan.

Biotransformation

Irbesartan is metabolised by the liver via glucuronide conjugation and oxidation. The primary metabolite is the inactive irbesartan glucuronide conjugate and accounts for approximately 6 % of circulating metabolites. The remaining oxidative metabolites are considered to be inactive. *In vitro* studies indicate that irbesartan is oxidised primarily by the cytochrome P450 2C9 isoenzyme. Isoenzyme 3A4 has negligible effect. It is not metabolised by, nor does it substantially induce or inhibit most isoenzymes commonly associated with medicine metabolism (i.e. 1A1, 1A2, 2A6, 2B6, 2D6 or 2E1). Irbesartan does not induce or inhibit

isoenzyme 3A4.

Elimination

The glucuronide conjugate is cleared by renal elimination (20 %) and biliary excretion (80 %). The terminal elimination half-life ranges from 11 to 15 hours. The plasma clearance of irbesartan is unaffected by either renal or mild to moderate hepatic insufficiency. Steady state plasma concentrations are attained within 3 days after initiation of a once-daily dosing regimen.

Linearity/non-linearity

Irbesartan exhibits linear pharmacokinetics over the therapeutic dose range. Steady-state plasma concentrations are attained within 3 days after initiation of a once-daily dosing regimen. Limited accumulation (< 20 %) is observed in plasma upon repeated once-daily dosing.

Pharmacokinetics in special patient groups

Hepatic impairment

In patients with mild to moderate cirrhosis, the pharmacokinetics of irbesartan are not significantly altered.

Renal impairment

In patients with renal impairment (regardless of degree) or those undergoing haemodialysis, the pharmacokinetics of irbesartan are not significantly altered. Irbesartan is not removed by haemodialysis.

Hypertensive patients

In male and female hypertensive patients, higher (11 - 44 %) plasma concentrations of irbesartan were observed in females than in males, although, following multiple dosing, males and females did not show differences in either accumulation or elimination half-life. No gender-specific differences in clinical effect have been observed.

Elderly

In elderly (male and female) normotensive subjects (65 - 80 years) with clinically normal renal and hepatic function, the plasma AUC and peak plasma concentrations (C_{max}) of irbesartan are approximately 20 - 50 % greater than those observed in younger subjects (18 - 40 years). Regardless of age, the elimination half-life is comparable. No significant age-related differences in clinical effect have been observed.

Ethnicity

In black and white normotensive subjects, the plasma AUC and t½ of irbesartan are approximately 20 - 25 % greater in blacks than in whites; the peak plasma concentrations (C_{max}) of irbesartan are essentially equivalent.

5.3 Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal anhydrous silica

Hydrogenated castor oil

Lactose monohydrate

Magnesium stearate

Maize starch

Microcrystalline cellulose

Povidone

Sodium croscarmellose.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

60 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the blister in the outer carton until required for use.

6.5 Nature and contents of container

DYNARB 150 mg and 300 mg:

White opaque PVC/PVDC/ aluminium foil blisters. 5 tablets are placed into a blister strip. 6 x 5 tablets with a package insert are placed in a printed cardboard carton.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Pharma Dynamics (Pty) Ltd

1st Floor, Grapevine House, Steenberg Office Park

Silverwood Close

Westlake, Cape Town

7945, South Africa

Tel.: +27 21 707 7000

or 0860-PHARMA (742 762)

8. REGISTRATION NUMBER(S)

DYNARB 150 mg: RSA: A43/7.1.3/0720

DYNARB 300 mg: RSA: A43/7.1.3/0721

9. DATE OF FIRST AUTHORISATION

07 June 2012

10. DATE OF REVISION OF THE TEXT

09 May 2025

DYNARB 150 mg: NAM: 12/7.1.3/0223

DYNARB 300 mg: NAM: 12/7.1.3/0224