Package insert for VALHEFT 40, 80 and 160

SCHEDULING STATUS

S3

PROPRIETARY NAME AND DOSAGE FORM

VALHEFT 40 film coated tablet

VALHEFT 80 film coated tablet

VALHEFT 160 film coated tablet

COMPOSITION

VALHEFT 40: Each film coated tablet contains 40 mg valsartan.

VALHEFT 80: Each film coated tablet contains 80 mg valsartan.

VALHEFT 160: Each film coated tablet contains 160 mg valsartan.

Inactive ingredients:

Anhydrous lactose, crospovidone, magnesium stearate, microcrystalline cellulose and silica.

VALHEFT 40 and **160** also contain Opadry Yellow (consisting of hypromellose, macrogol, titanium dioxide and yellow iron oxide).

VALHEFT 80 also contains Opadry Pink (consisting of hypromellose, macrogol, titanium dioxide, red iron oxide and yellow iron oxide).

Contains sugar (anhydrous lactose).

PHARMACOLOGICAL CLASSIFICATION

A 7.1.3 Vascular medicine - other hypotensives

PHARMACOLOGICAL ACTION

Pharmacodynamic properties:

Valsartan is a non-peptide angiotensin II receptor antagonist that selectively blocks the binding of angiotensin II to the AT_1 receptor in tissues such as vascular smooth muscle and the adrenal gland. In the renin-angiotensin system, angiotensin I is converted by angiotensin-converting enzyme (ACE) to form angiotensin II. Angiotensin II stimulates the adrenal cortex to synthesise and secrete aldosterone, which decreases the excretion of sodium and increases the excretion of potassium. Angiotensin II also acts as a vasoconstrictor in vascular smooth muscle. Valsartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by inhibiting the binding of angiotensin II to the AT_1 receptor.

Pharmacokinetic properties:

Valsartan is well absorbed after oral administration, with a bioavailability of approximately 23 %. Peak plasma concentrations occur 2 to 4 hours after an oral dose. Valsartan shows multi-exponential decay kinetics ($t_{½}$ α < 1 h and $t_{½}$ β about 9 h).

The pharmacokinetics of valsartan is linear in the dose range tested. There is no change in the kinetics of valsartan on repeated administration and little accumulation when dosed once daily. Plasma concentrations are similar in males and females.

Valsartan is highly bound to serum protein (94 to 97 %), mainly serum albumin. Steady-state volume of distribution is low (about 17 ℓ). Plasma clearance is relatively slow (about 2 ℓ/h) when compared with hepatic blood flow (about 30 ℓ/h).

Valsartan is not significantly metabolised and is excreted mainly unchanged via the bile Following an oral dose about 70 % is excreted in the faeces and 30 % in urine.

The mean elimination half-life is about 9 hours.

When valsartan is given with food, the area under the plasma concentration curve (AUC) of valsartan is reduced by 48 %, although from about 8 hours post dosing plasma valsartan concentrations are similar for the fed and fasted group. This reduction in AUC, however, is not

accompanied by a clinically significant reduction in the therapeutic effect, and valsartan can therefore be given either with or without food.

The average time to peak concentration and elimination half-life of valsartan in heart failure patients are similar to that observed in healthy volunteers. AUC and C_{max} values of valsartan increase linearly and are almost proportional with increasing dose over the clinical dosing range (40 mg to 160 mg twice a day). The average accumulation factor is about 1,7. The apparent clearance of valsartan following oral administration is approximately 4,5 ℓ/h. Age does not affect the apparent clearance in heart failure patients.

Elderly patients:

A significantly higher systemic exposure to valsartan was observed in elderly subjects than in young subjects; however, this has not been shown to have any clinical significance.

Renal impairment:

Renal clearance accounts for only 30 % of total plasma clearance and no correlation is seen between renal function and systemic exposure to valsartan. Dose adjustment is therefore not required in patients with mild renal impairment. No studies have been performed in patients undergoing dialysis. However, valsartan is highly bound to plasma protein and is unlikely to be removed by dialysis.

Hepatic impairment:

About 70 % of the absorbed dose is excreted in the bile mainly as unchanged compound. Valsartan does not undergo extensive biotransformation and systemic exposure to valsartan is not correlated with the degree of liver dysfunction. No dose adjustment for valsartan is therefore necessary in patients with hepatic insufficiency of non-biliary origin and without cholestasis. The AUC with valsartan has been observed to be approximately double in patients with biliary cirrhosis or biliary obstruction (see **WARNINGS AND SPECIAL PRECAUTIONS**).

INDICATIONS

Hypertension: Treatment of mild to moderate hypertension.

Heart failure: Treatment of heart failure (NYHA class II - IV).

CONTRAINDICATIONS

- Hypersensitivity to valsartan or any of the excipients of **VALHEFT** (see **COMPOSITION**).
- Pregnancy and lactation (see **PREGNANCY AND LACTATION**).
- Severe renal function impairment (creatinine clearance less than 30 ml/min).
- A history of angioedema related to previous therapy with angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs): These patients must never again be given these medicines.
- Hereditary or idiopathic angioedema.
- Hypertrophic obstructive cardiomyopathy (HOCM).
- Bilateral renal artery stenosis.
- Renal artery stenosis in patients with a single kidney.
- Aortic stenosis.
- Concomitant therapy with potassium-sparing diuretics, such as spironolactone, triamterene, and amiloride (see **INTERACTIONS**).
- Porphyria.
- Lithium therapy: Concomitant administration with **VALHEFT** may lead to toxic blood concentrations of lithium (see **INTERACTIONS**).
- The concomitant use of **VALHEFT** with aliskiren-containing products is contraindicated (see **WARNINGS AND SPECIAL PRECAUTIONS** and **INTERACTIONS**).

WARNINGS AND SPECIAL PRECAUTIONS

Should a woman become pregnant while receiving **VALHEFT**, the treatment should be stopped promptly and switched to a different class of antihypertensive medicine.

Should a woman contemplate pregnancy, the doctor should consider alternative medication. (See **CONTRAINDICATIONS** and **PREGNANCY AND LACTATION**.)

Hypotension and electrolyte/fluid imbalance:

Sodium- and/or volume-depletion, due to excessive perspiration, vomiting, diarrhoea, prolonged diuretic therapy, dialysis or dietary salt restriction may increase the risk of symptomatic hypotension. In sodium-depleted and/or volume-depleted patients, such as those receiving high doses of diuretics, and/or patients with moderate to severe renal impairment, symptomatic hypotension may occur after initiation of therapy with **VALHEFT**. Sodium- and/or volume-depletion should be corrected before starting treatment with **VALHEFT** (for example, by reducing the diuretic dose).

If hypotension occurs, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. Treatment can be continued once blood pressure has stabilised.

Renal artery stenosis:

Short-term administration of **VALHEFT** to patients with renovascular hypertension secondary to unilateral renal artery stenosis, did not induce any significant changes in renal haemodynamics or serum creatinine. However, since other medicines that affect the renin-angiotensin-aldosterone system may increase blood urea and serum creatinine in patients with bilateral or unilateral renal artery stenosis, monitoring of both parameters is recommended as a safety measure (see **CONTRAINDICATIONS**).

Renal impairment:

No dosage adjustment is required for patients with mild to moderate renal impairment. However, in severe cases (creatinine clearance < 30 ml/min) insufficient data are available. **VALHEFT** should not be used because of increased side effects (see **CONTRAINDICATIONS**).

Hepatic impairment:

No dosage adjustment is required for patients with hepatic insufficiency of non-biliary origin and without cholestasis. **VALHEFT** is mostly eliminated unchanged in the bile, and patients with biliary obstructive disorders showed lower valsartan clearance (see **Pharmacokinetic properties**). Caution should be exercised when using **VALHEFT** in patients with biliary obstructive disorders. **VALHEFT** is not recommended for use in patients with severe hepatic impairment.

Hyperkalaemia:

Since hyperkalaemia may occur, serum potassium concentrations should be monitored, especially in the elderly and patients with renal impairment and the concomitant use of potassium-sparing diuretics should generally be avoided (see **CONTRAINDICATIONS** and **INTERACTIONS**).

Heart failure:

Use of **VALHEFT** in patients with heart failure commonly results in some reduction in blood pressure, but discontinuation of **VALHEFT** therapy because of continuing symptomatic hypotension is not usually necessary provided dosing instructions are followed. Caution should be observed when initiating therapy in patients with heart failure (see **DOSAGE AND DIRECTIONS FOR USE**).

In patients with heart failure, caution should be observed with concurrent administration of ACE inhibitors, beta-blockers and **VALHEFT** as an increase in mortality has been reported on this triple therapy (see **INTERACTIONS**).

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

VALHEFT and aliskiren is therefore contraindicated (see **CONTRAINDICATIONS** and **INTERACTIONS**).

VALHEFT should not be used concomitantly with aliskiren (see **CONTRAINDICATIONS**).

In patients with severe heart failure whose renal function may depend on the activity of the RAAS, treatment with ACE inhibitors or angiotensin receptor antagonists has been associated with oliguria and/or progressive uraemia and with acute renal failure and/or death. Evaluation of patients with heart failure should always include assessment of renal function.

Effects on ability to drive and use machines:

It is advisable to exercise caution when driving, operating machinery or performing tasks requiring alertness, until the effects of **VALHEFT** are known.

Contains sugar (anhydrous lactose):

Patients with the rare hereditary conditions of lactose or galactose intolerance, e.g. galactosaemia, Lapp lactase deficiency, or glucose-galactose malabsorption should not take **VALHEFT**.

INTERACTIONS

- 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 aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (see **CONTRAINDICATIONS**, **WARNINGS AND SPECIAL PRECAUTIONS**).
- Concomitant use of potassium-sparing diuretics, potassium supplements or salt substitutes containing potassium may lead to increased serum potassium and in heart failure patients to increase serum creatinine levels (see **CONTRAINDICATIONS**).

- As **VALHEFT** is not metabolised to a significant extent, clinically relevant interactions in the form of metabolic induction or inhibition of the cytochrome P450 isoenzyme system is not expected.
- The antihypertensive effects of **VALHEFT** may be potentiated by medicines that lower blood pressure.
- Increased mortality has been reported with valsartan in patients with heart failure also receiving both ACE inhibitors and beta blockers and it should be avoided in such patients (see **WARNINGS AND SPECIAL PRECAUTIONS**).
- Concurrent use of **VALHEFT** with lithium may reduce lithium clearance and result in lithium toxicity. Lithium levels should be regularly monitored (see **CONTRAINDICATIONS**).
- Nonsteroidal anti-inflammatory medicine (NSAIDs), including cyclo-oxygenase-2 inhibitors, may reduce the effect of diuretics and the antihypertensive effect of **VALHEFT**. Patients taking NSAIDs concomitantly with **VALHEFT** should be adequately hydrated and renal function should be monitored.
- No interactions of clinical significance have been found during clinical trials with the following compounds: cimetidine, warfarin, furosemide, digoxin, atenolol, indomethacin, hydrochlorothiazide, amlodipine and glibenclamide.

PREGNANCY AND LACTATION

Pregnancy:

Safety has not been established. **VALHEFT** is not to be used in pregnancy (see **CONTRAINDICATIONS**). Medicines affecting the renin-angiotensin system, such as **VALHEFT**, can cause embryonal toxicity, foetal and neonatal morbidity and mortality when administered to pregnant women. When pregnancy is planned or confirmed, **VALHEFT** should be discontinued as soon as possible.

Women of childbearing age should ensure adequate contraception.

Lactation:

Safety has not been established. **VALHEFT** should not be used during breastfeeding (see **CONTRAINDICATIONS**).

DOSAGE AND DIRECTIONS FOR USE

VALHEFT can be taken with or without food.

Hypertension:

The recommended dose of **VALHEFT** is 80 mg or 160 mg once daily, irrespective of race, age or gender.

The antihypertensive effect is substantially present within 2 weeks and maximal effects are seen after 4 weeks. In patients whose blood pressure is not adequately controlled, the daily dose may be increased to 320 mg, or a diuretic may be added.

VALHEFT may also be administered with other antihypertensive medicines.

Heart failure:

The recommended starting dose of **VALHEFT** is 40 mg twice daily. Up-titration to 80 mg and 160 mg twice daily should be done to the highest dose, tolerated by the patient. Consideration should be given to reducing the dose of concomitant diuretics. The maximum daily dose administered is 320 mg in divided doses.

Evaluation of patients with heart failure should always include assessment of renal function.

NOTE for all indications:

No initial dosage adjustment is required for patients with mild renal impairment (where the creatinine clearance is above 70 ml/min) or for patients with hepatic insufficiency of non-biliary origin and without cholestasis.

VALHEFT is contraindicated in patients with severe renal impairment.

Use in children and adolescents:

The safety and efficacy of **VALHEFT** have not been established in children and adolescents (below the age of 18 years).

SIDE EFFECTS

Infections and infestations:

Frequent: viral infections

Less frequent: upper respiratory tract infection, pharyngitis, sinusitis, rhinitis

Blood and the lymphatic system disorders:

Frequent: neutropenia

Less frequent: thrombocytopenia

Immune system disorders:

Less frequent: hypersensitivity including serum sickness

Metabolism and nutrition disorders:

Less frequent: hyperkalaemia

Psychiatric disorders:

Less frequent: insomnia, decreased libido

Nervous system disorders:

Frequent: postural dizziness

Less frequent: syncope, dizziness, headache

Eye disorders:

Less frequent: blurred vision

Ear and labyrinth disorders:

Less frequent: vertigo

Cardiac disorders:

Less frequent: cardiac failure

Vascular disorders:

Frequent: postural (orthostatic) hypotension

Less frequent: hypotension (may occur in patients with volume depletion), vasculitis

Respiratory, thoracic and mediastinal disorders:

Less frequent: cough

Gastrointestinal disorders:

Less frequent: diarrhoea, abdominal pain, nausea

Hepatobiliary disorders:

Frequency unknown: hepatitis

Skin and subcutaneous tissue disorders:

Less frequent: angioedema, rash, pruritus, urticaria

Musculoskeletal, connective tissue and bone disorders:

Less frequent: back pain, arthralgia, myalgia, rhabdomyolysis

Renal and urinary disorders:

Less frequent: renal impairment, acute renal failure, renal insufficiency

General disorders and administrative site conditions:

Less frequent: fatigue, asthenia, oedema

Frequency unknown: alopecia

Investigations:

Less frequent: Elevated liver enzymes. Decreased: haemoglobin, haematocrit, white blood cells; increased: serum creatinine, potassium, total bilirubin.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Symptoms:

Overdose with **VALHEFT** may result in marked hypotension, which could lead to depressed level of consciousness, circulatory collapse and/or shock. Bradycardia or tachycardia may also occur with **VALHEFT** overdose.

Treatment:

If the ingestion is recent, vomiting should be induced. Otherwise, the usual treatment would be intravenous infusion of normal saline solution. It is unlikely to be removed by haemodialysis.

IDENTIFICATION

VALHEFT 40: Yellow coloured, round, biconvex, film coated tablets debossed with 'J' on one side and '40' on the other.

VALHEFT 80: Peach coloured, round, biconvex, film coated tablets, scored on one side and debossed with '80' on scored side and 'J' on the other.

VALHEFT 160: Yellow coloured, oval shaped, biconvex, film coated tablets, scored on one side and debossed with '160' on scored side and 'J' on the other.

PRESENTATION

2 x blister strips each containing 14 tablets are placed into a carton box (28 tablets per pack).

The blister strips are comprised of aluminium foil and a multilayer base film (OPA/aluminium foil/PVC).

STORAGE INSTRUCTIONS

Store at or below 25 °C.

Keep blister strips in outer carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS

VALHEFT 40: 46/7.1.3/0743

VALHEFT 80: 46/7.1.3/0744

VALHEFT 160: 46/7.1.3/0745

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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DATE OF PUBLICATION OF THE PACKAGE INSERT

27 July 2017.