**SCHEDULING STATUS:** **S3**

**PROPRIETARY NAMES AND DOSAGE FORM:**

ZOMEVEK 80 TABLET (film-coated tablet)

ZOMEVEK 160 TABLET (film-coated tablet)

**COMPOSITION:**

Zomevek 80 Tablet: Each film coated tablet contains 80 mg valsartan.

Zomevek 160 Tablet: Each film coated tablet contains 160 mg valsartan.

**List of excipients:**

Microcrystalline cellulose, crospovidone, colloidal anhydrous silica, magnesium stearate, hypromellose, macrogol 8000, red iron oxide, yellow iron oxide, black iron oxide (160 mg only), titanium dioxide.

The tablets are sugar free.

**PHARMACOLOGICAL CLASSIFICATION:**

A 7.1.3 Vascular medicines – other hypotensives

**PHARMACOLOGICAL ACTION:**

Valsartan is an orally active, specific angiotensin II (Ang II) receptor antagonist. It acts selectively on the Angiotensin I receptor subtype, which is responsible for the known actions of Angiotensin II. The increased plasma levels of Angiotensin II following Angiotensin I receptor blockade with valsartan may stimulate the unblocked Angiotensin II receptor, which appears to counterbalance the effect of the Angiotensin I receptor. Valsartan does not exhibit any partial agonist activity at the Angiotensin I receptor and has much greater affinity (about 20 000 fold) for the Angiotensin I receptor than for the Angiotensin II receptor.

The Angiotensin II receptor subtype is unrelated to cardiovascular effect.

**Hypertension:**

Administration of valsartan to patients with hypertension results in reduction of blood pressure without affecting pulse rate.

In most patients, after administration of a single oral dose, onset of antihypertensive activity occurs within 2 hours and the peak reduction of blood pressure is achieved within 4 to 6 hours. The antihypertensive effect persists for over 24 hours after dosing. During repeated dosing, the maximum reduction in blood

pressure with any dose is generally attained within 2 to 4 weeks and is sustained during long-term therapy.

Abrupt withdrawal of valsartan has not been associated with rebound hypertension or other adverse clinical events.

**Pharmacokinetics:**
Valsartan is absorbed after oral administration, although the amount absorbed varies widely. Mean absolute bioavailability for valsartan is 23 %. Valsartan shows multi-exponential decay kinetics ($t_{½}\ \alpha$ < 1 h and $t_{½}\ \beta$ 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). Of the absorbed dose of valsartan 70 % is excreted in the faeces and after IV administration, 30 % in the urine, mainly as unchanged compound.

When valsartan is given with food, the area under the plasma concentration curve (AUC) of valsartan is reduced by 48 %, although from about 8 h 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.

***Elderly:***
A significantly higher systemic exposure to valsartan was observed in elderly patients.

***Impaired Renal Function:***
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. 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:**

ZOMEVEK is indicated for the treatment of mild to moderate hypertension.

**CONTRA INDICATIONS:**

Hypersensitivity to valsartan or any of the excipients of ZOMEVEK.

The use of ZOMEVEK during pregnancy and lactation is contra-indicated (see “Pregnancy and lactation”). ZOMEVEK should be discontinued as soon as pregnancy is suspected.

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.

Lithium therapy: Concomitant administration with ZOMEVEK may lead to toxic blood concentrations of lithium.

Safety and efficacy have not been established in children.

Safety in porphyria has not been established.

Hereditary or idiopathic angioedema.

Hypertrophic obstructive cardiomyopathy (HOCM).

Moderate to severe renal function impairment (creatinine clearance less than 30 mℓ /min).

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, amiloride.

**WARNINGS AND SPECIAL PRECAUTIONS:**

ZOMEVEK should be used with caution in patients with bilateral renal artery stenosis or stenosis of an artery to a single kidney, aortic valve stenosis or hypertrophic obstructive cardiomyopathy. Short-term administration of ZOMEVEK 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 agents 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.

**Sodium- and/or volume-depleted patients:** 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 ZOMEVEK. Sodium- and/or volume-

depletion should be corrected before starting treatment with ZOMEVEK 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.

Women of childbearing age should ensure adequate contraception. ZOMEVEK is contra-indicated in pregnancy and should be used with care if at all, during breastfeeding.

**Impaired renal function:** No dosage adjustment is required for patients with mild renal impairment. However, in moderate to severe cases (creatinine clearance < 70 mℓ /min), ZOMEVEK should not be used because of increased side-effects.
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 be avoided (see “Interactions”).

**Hepatic impairment:** Reduced doses must be considered in patients with hepatic impairment. ZOMEVEK is mostly eliminated unchanged in the bile, and patients with biliary obstructive disorders showed lower ZOMEVEK clearance (see “Pharmacokinetics”). Particular caution should be exercised when administering valsartan to patients with biliary obstructive disorders. Halving of the dose should also be considered for patients with a history of hepatic impairment (see “Dosage and directions for use”).

As a consequence of inhibiting the renin-angiotensin-aldosterone system (RAAS), changes in renal function may be anticipated in susceptible individuals. 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 azotaemia and with acute renal failure and/or death. Evaluation of patients with post-myocardial infarction and heart failure should always include assessment of renal function.
In patients with heart failure, caution should be observed with concurrent administration of ACE inhibitors, beta-blockers and ZOMEVEK as an increase in mortality has been reported on this triple therapy (see “Interactions”).

**Effects on ability to drive and use machines:**
It is advisable to exercise caution when driving or operating machinery.

**INTERACTIONS:**
No substance interactions of clinical significance have been found. Compounds studied in clinical trials include: cimetidine, warfarin, furosemide, digoxin, atenolol, hydrochlorothiazide, amlodipine and

glibenclamide.
Non-steroidal anti-inflammatory agents (NSAID's) may antagonise the antihypertensive effect of ZOMEVEK.
As ZOMEVEK is not metabolised to a significant extent, clinically relevant substance-substance interactions in the form of metabolic induction or inhibition of the cytochrome P450 system are not expected with valsartan. Although valsartan is highly bound to plasma proteins, *in vitro* studies have not shown any interaction at this level with a range of molecules which are also highly protein-bound, such as diclofenac, furosemide and warfarin.
Concurrent use with sympathomimetics may reduce the antihypertensive effect of ZOMEVEK.
Concomitant use of potassium-sparing diuretics (e.g. spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium, and in heart failure patients to increase in serum creatinine. If co-medication is considered necessary, caution is advisable. Increased mortality has been reported with ZOMEVEK in patients with heart failure also receiving ACE inhibitors or beta-blockers. Concurrent use of ZOMEVEK is not recommended in these patients (see "Warnings and special precautions").

**PREGNANCY AND LACTATION:**
When pregnancy is detected, ZOMEVEK should be discontinued as soon as possible. Not to be used in pregnancy as teratogenicity has been shown in experimental animals.
Safety in pregnancy and lactation has not been established.

**DOSAGE AND DIRECTIONS FOR USE:**
**Hypertension:**
The recommended dose of ZOMEVEK is 80 mg or 160 mg once daily. 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.
ZOMEVEK may also be administered with other antihypertensive agents.
ZOMEVEK may be administered with or without food.
**NOTE:** No dosage adjustment is required for patients with mild renal impairment (where the creatinine clearance is above 70 mℓ /min). A lower dose should be considered for patients with a history of hepatic impairment (see "Warnings and special precautions").

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

**SIDE EFFECTS:**

Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1 000, < 1/100); rare (≥ 1/10 000, < 1/1 000); very rare (< 1/10 000).

***Table 1:***

| | |
|---|---|
| **Infections and infestations:** | |
| ***Common:*** | Viral infections |
| ***Uncommon:*** | Upper respiratory tract infection, pharyngitis, sinusitis |
| ***Very rare:*** | Rhinitis |
| **Blood and lymphatic system disorders:** | |
| ***Common:*** | Neutropenia |
| ***Very rare:*** | Thrombocytopenia |
| **Immune system disorders:** | |
| ***Very rare:*** | Hypersensitivity including serum sickness |
| **Metabolism and nutrition disorders:** | |
| ***Uncommon:*** | Hyperkalaemia |
| **Psychiatric disorders:** | |
| ***Uncommon:*** | Insomnia, libido decrease |
| **Nervous system disorders:** | |
| ***Common:*** | Postural dizziness |
| ***Uncommon:*** | Syncope |
| ***Rare:*** | Dizziness |
| ***Very rare:*** | Headache |
| **Ear and labyrinth disorders:** | |
| ***Uncommon:*** | Vertigo |
| **Cardiac disorders:** | |
| ***Uncommon:*** | Cardiac failure |
| **Vascular disorders:** | |
| ***Common:*** | Orthostatic hypotension |
| ***Uncommon:*** | Hypotension |
| ***Very rare:*** | Vasculitis |
| **Respiratory, thoracic and mediastinal disorders:** | |
| ***Uncommon:*** | Cough |
| **Gastrointestinal disorders:** | |
| ***Uncommon:*** | Diarrhoea, abdominal pain |
| ***Very rare:*** | Nausea |
| **Skin and subcutaneous tissue disorders:** | |

| | |
|---|---|
| ***Very rare:*** | Angioneurotic oedema, rash, pruritus, Henöch-Schonlein purpura, psoriasis |
| **Musculoskeletal and connective tissue disorders:** | |
| ***Uncommon:*** | Back pain |
| ***Very rare:*** | Arthralgia, myalgia |
| **Renal and urinary disorders:** | |
| ***Very rare:*** | Renal impairment, acute renal failure, renal insufficiency |
| **General disorders and administration site conditions:** | |
| ***Uncommon:*** | Fatigue, asthenia, oedema |

**Laboratory findings:**

ZOMEVEK may be associated with decreases in haemoglobin and haematocrit.

Neutropenia was observed in 1,9 % of patients treated with ZOMEVEK.

In controlled clinical trials in hypertensive patients, significant increases in serum creatinine, potassium and total bilirubin were observed, respectively, in 0,8 %, 4,4 %, and 6 % of patients treated with ZOMEVEK.

No special monitoring of laboratory parameters is necessary for patients with essential hypertension receiving ZOMEVEK therapy.

Elevations of liver function values were reported in hypertensive patients treated with ZOMEVEK.

**KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:**

Overdose with ZOMEVEK may result in marked hypotension, which could lead to depressed levels of consciousness, circulatory collapse and/or shock. If the ingestion is recent, vomiting should be induced. Otherwise, the usual treatment would be intravenous infusion of normal saline solution.

ZOMEVEK is unlikely to be removed by haemodialysis.

**IDENTIFICATION:**

**Zomevek 80 Tablet**:

Pale red, round film-coated tablet with bevelled edges, one side with debossing ‘DV” and “NVR” on the reverse side of the tablet. Film-coating is intact and shows no signs of cracks.

**Zomevek 160 Tablet**:

Grey-orange, ovaloid film-coated tablet, slightly convex, one side with debossing **“**DX**”** and “NVR” on the reverse side of the tablet. Film-coating is intact and shows no signs of cracks.

**PRESENTATION:**

7, 10, 14, 15, 20, 28, 30, 50, 56, 60, 84, 90, 98, 100 or 28 tablets in PVC/PE/PVDC aluminium foil blisters (Triplex) or PA/AL/PVC aluminium foil blisters (alu-alu or double-sided aluminium blisters) or PVC/PVDC with aluminium foil (Duplex) blisters.

The aluminium foil is silver and the PVC/PVDC is clear, colourless and transparent.

The outer container is a printed cardboard box.

Not all pack sizes may be marketed.

**STORAGE INSTRUCTIONS:**

Store at or below 25 °C. Protect from moisture.

Keep the blisters in the outer carton until required for use, to protect the tablets from moisture.

**KEEP OUT OF REACH OF CHILDREN.**

**REGISTRATION NUMBER:**

Zomevek 80 Tablet: 43/7.1.3/0036

Zomevek 160 Tablet: 43/7.1.3/0037

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

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**DATE OF PUBLICATION:**

Date of registration: 23 July 2010

Date of most recent approval of professional information: 23 July 2010

**Additional countries registration details:**

| *Country* | *Product name* | *Scheduling status (or Category of distribution)* | *Registration number* |
|---|---|---|---|
| **Namibia** | Zomevek 80 | NS2 | 12/7.1.3/0022 |
| | Zomevek 160 | NS2 | 12/7.1.3/0023 |
| **Zambia** | Zomevek 80 | POM | 039/048 |
| | Zomevek 160 | POM | 039/049 |

*ATC Code:* C09CA03 – Angiotensin II antagonists, plain

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