Hypertension
NSAIDs may lead to the onset of new hypertension or worsening the pre-existing hypertension and patients taking antihypertensive with NSAIDs may have an impaired anti-hypertensive response. Caution is advised when prescribing NSAIDs to patients with hypertension. Blood pressure should be monitored closely during initiation of NSAID treatment and at regular intervals thereafter.

Gastrointestinal bleeding, ulceration and perforation
GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at any time during treatment, with or without warning symptoms or a previous history of serious GI events. Debilitated patients seems to tolerate ulceration or bleeding less well than others. Most of the fatal gastrointestinal events associated with NSAIDs occurred in the elderly and/or debilitated patients. The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation, and in the elderly. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin, or other drugs likely to increase gastrointestinal risk. Naproxen has been found to be well tolerated by patients exhibiting dyspepsia with other similar agents. Nonetheless, episodes of gastro-intestinal bleeding have been reported in patients with naproxen therapy. Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment. Caution should be advised in patients receiving concomitant medications, which could increase the risk of ulceration, or bleeding, such as corticosteroids, or anticoagulants such as warfarin, selective serotonin reuptake inhibitors or antiplatelet agents such as aspirin. When GI bleeding or ulceration occurs in patients receiving naproxen, the treatment should be withdrawn. Naproxen should be given with care to patients with a history of inflammatory bowel disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated. In patients with a history of gastrointestinal disease, naproxen should be given under close supervision. As with other NSAIDs, the incidence and severity of gastrointestinal complications may increase with increasing dose and duration of treatment with naproxen.

Severe Skin Reactions
Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs. Patients appear to be at highest risk for these reactions early in the course of therapy: the onset of the reactions occurring in the majority of cases within the first month of treatment. Naproxen should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

WARNINGS
RISK OF GI ULCERATION, BLEEDING AND PERFORATION WITH NSAID.
Serious GI toxicity such as bleeding, ulceration and perforation can occur at any time, with or without warning symptoms, in patients treated with NSAID therapy. Although minor upper GI problems (e.g. Dyspepsia) are common, usually developing early in therapy, prescribers should remain alert for ulceration and bleeding in patients treated with NSAIDs even in the absence of previous GI tract symptoms.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Patients with prior history of serious adverse events and other risk factors associated with peptic ulcer disease (e.g. Alcoholism, smoking and corticosteroid therapy) are at increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less than other individuals and account for most spontaneous reports for fatal GI events.

INTERACTIONS WITH OTHER MEDICAMENTS
Probenecid
Caution is advised when probenecid is administered concurrently since probenecid increases naproxen plasma concentrations and increases the half-life considerably.
Methotrexate
Decreased elimination of methotrexate. Caution is advised when methotrexate is administered concurrently because of possible enhancement of its toxicity.
Anti-hypertensives
Reduced anti-hypertensive effect. Naproxen and other NSAID drugs can reduce the effect of beta blockers, ACE inhibitors, and ARBs. Concomitant use of NSAIDs with ACE inhibitors or angiotensin-II receptor antagonists may increase the risk of renal impairment, especially in patients with pre-existing poor renal function.
Cyclosporin
Concurrent use of cyclosporin with an NSAID may increase the risk of renal failure.
Diuretics
Reduced diuretic effect. Diuretics can increase the risk of nephrotoxicity of NSAIDs. The natriuretic effect of furosemide has been reported to be inhibited by some drugs of this class.
Cardiac glycosides
NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels.
Lithium
Decreased elimination of lithium. Inhibition of renal lithium clearance leading to increase in plasma lithium concentration has been reported.
Mifepristone
NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.
Corticosteroids
Increased risk of GI bleeding or gastrointestinal ulceration.
Anticoagulants
It is considered unsafe to take NSAIDs in combination with anti-coagulants such as warfarin or heparin unless under direct medical supervision, as NSAIDs may enhance the effects of anti-coagulants. Naproxen decreases platelet aggregation and prolongs bleeding time. This effect should be kept in mind when bleeding times are determined. Due to the plasma protein binding of naproxen, patients simultaneously receiving anticoagulants should be observed for signs of overdosage of these drugs.
Quinolone antibiotics
NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.
Tacrolimus
Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.
Sulfonamides and hydantoins
Naproxen is highly bound to plasma albumin; thus, it has a theoretical potential for interaction with other albumin-bound drugs such as coumarin-type anticoagulants, sulfonylureas, hydantoins, other NSAIDs and aspirin. Concurrent administration of hydantoin, sulfonamide or sufonylurea with naproxen should be observed for dose adjustments if required. Caution is advised for concomitant administration of glimepiride or Glipizide since interaction has been seen with other non-steroidal agents of this class.

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs)
There is an increased risk of gastrointestinal bleeding when anti-platelet agents and SSRIs are combined with NSAIDs.

RECOMMENDED DOSAGE
General
Although naproxen and naproxen-sodium-containing products all circulate in the plasma as naproxen, they have pharmacokinetic differences that may affect onset of action. Onset of pain relief can begin within 30 minutes in patients taking naproxen sodium and within 1 hour in patients taking naproxen.

The recommended strategy for initiating therapy is to choose a formulation and a starting dose likely to be effective for the patient and then adjust the dosage based on observation of benefit and/or adverse events.

A lower dose should be considered in patients with renal or hepatic impairment or in elderly patients. Safrosyn S Tablet is not recommended in patients with baseline creatinine clearance less than 20ml/minute because accumulation of naproxen metabolites has been seen in such patients.

Recommended formulations
Because the sodium salt of naproxen is more rapidly absorbed, Safrosyn S Tablet is recommended for the management of acute painful conditions when prompt onset of pain relief is desired. Safrosyn S Tablet may be given orally either in fasting state or with meals and/or antacids.

Dose in adults
Analgesia / Dysmenorrhea / Acute musculoskeletal conditions/ Acute pain states in which there is an inflammatory component:
Because the sodium salt of naproxen is more rapidly absorbed, Safrosyn S Tablet is recommended for the management of acute painful conditions when prompt onset of pain relief is desired. The recommended starting dose is 550 mg followed by 275 mg every 6-8 hours as required.

Acute gout
The recommended starting dose is 825 mg followed by 275 mg every 8 hours as needed.

Migraine
For treatment of acute migraine headache, the recommended dose is 825 mg at the first symptom of an impending attack. An additional dose of Safrosyn S Tablet 275 mg to 550 mg can be taken throughout the day, if necessary, but not before half an hour after the initial dose. For prophylaxis of migraine headache, the dose is 550 mg twice daily. If no improvement is seen within 4 to 6 weeks, the drug should be discontinued. A total daily dose of 1375mg per day should not be exceeded.

Dose in children
Not recommended for use in children below 16 years of age.

OVERDOSE AND TREATMENT
Symptoms : Symptoms include headache, nausea, vomiting, indigestion, epigastric pain, gastrointestinal bleeding, abdominal discomfort, rarely diarrhoea,heartburn, disorientation, excitation, drowsiness, dizziness, tinnitus, fainting, transient alterations in liver function, hypoprothrombinemia, metabolic acidosis, apnoea, or disorientation. Because naproxen may be rapidly absorbed, high and early blood levels should be anticipated. In cases of significant poisoning acute renal failure and liver damage are possible. Hypertension, acute renal failure, respiratory depression and coma may occur after the ingestion of NSAIDs but are rare. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following an overdose.

Treatment: Patients should be treated symptomatically as required. Stomach may be emptied and usual supportive measures employed. Prevention of further absorption (e.g. activated charcoal) may be indicated in patients seen within 4 hours of ingestion with symptoms or following a large overdose. Alternatively, in adults, gastric lavage should be considered within one hour of ingestion of a potentially life-threatening overdose. Good urine output should be ensured. Patients should be observed for at least four hours after ingestion of potentially toxic amounts. Frequent or prolonged convulsions should be treated with intravenous diazepam. Forced diuresis, haemodialysis or hemoperfusion does not decrease the plasma concentration of naproxen because of the high degree of protein binding.

ROUTE OF ADMINISTRATION
Oral.

STORAGE CONDITIONS
Store below 30°C, away from direct light.

SHELF LIFE
3 years from the date of manufacture.

DOSAGE FORMS AND PACKAGING AVAILABLE
In blisters of 500 tablets.

Date of revision: 13th May 2024

Product Registration Holder / Manufacturer:
Pharmaniaga Manufacturing Berhad (198001006232)
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43650 Bandar Baru Bangi, Selangor Darul Ehsan,
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RSBS23-T50-2405-08a

pharmaniaga®

SAFROSYN S TABLET

DESCRIPTION
Safrosyn S Tablet 275mg.
An oval, blue, film-coated tablet with 'SF' letters embedded on one side and plain on the other.

Each tablets contains:
Naproxen sodium 275 mg.

Safrosyn S Tablet 550 mg.
Blue, oblong, film-coated tablet with 'S' scored line 'F' on one side and plain on the other.

Each tablets contains:
Naproxen sodium 550 mg.

PHARMACODYNAMICS
Naproxen sodium is a non-steroidal anti-inflammatory drug (NSAID) with analgesic, anti-inflammatory and antipyretic properties.

PHARMACOKINETICS
Absorption
Naproxen sodium is absorbed rapidly and completely from the gastrointestinal tract after oral administration.
Concomitant administration of food can delay the absorption of naproxen, but does not affect its extend. Plasma levels and pain relief are achieved within 30 minutes after administration and peak plasma levels are reached in 1-2 hours, depending on the intake of food. naproxen sodium dissolves primarily in the small bowel rather than the stomach, so the absorption is delayed until the stomach is emptied.

Distribution
The distribution volume of naproxen is 0.16 l/kg. At therapeutic levels, naproxen is greater than 99% albumin-bound. There is less than proportional increase in plasma level at doses more than 500 mg/day due to an increase in clearance caused by saturation of plasma protein binding at higher doses. However, the concentration of unbound naproxen continues to increase proportionally to dose.

Steady-state plasma levels of naproxen are reached after 3-4 days. Naproxen enters synovial fluid, crosses the placenta and has been found in the milk of lactating mothers at a concentration approximately 1% of that found in plasma.

Metabolism
Naproxen sodium is extensively metabolised in the liver to 6-0-desmethyl naproxen.

Elimination
Approximately 95% of the naproxen from any dose is excreted in the urine, primarily as naproxen (less than 1%), 6-0-desmethyl naproxen (less than 1%), or their conjugates (66-92%). The rate of excretion of metabolites and conjugates has been found to coincide closely with the rate of naproxen disappearance from the plasma. Small amounts, 3% or less, are excreted in the faeces. The clearance of naproxen is approximately 0.13 ml/min/kg. The elimination half-life of naproxen is approximately 14 hours and independent of the chemical form or the formulation.

Pharmacokinetics in Special Populations

Renal impairment
Elimination of naproxen is decreased in patients with severe renal impairment due to potential accumulation of naproxen and metabolite in the kidney. The clearance of naproxen is greater than the estimated from the degree of renal impairment alone for patients with severely impaired renal (creatinine clearance less than 10 ml/min)

Children
In children aged 5 to 16 years, the pharmacokinetic profile of naproxen is similar to that in adults although the clearance is generally higher in children than in adults.

INDICATIONS
Naproxen sodium is indicated in the relief of mild to moderate pain including post partum pain, pain following IUD insertion, post-operative pain and pain due to orthopedic surgery, for the treatment of primary dysmenorrhea and for the relief (prophylaxis) of migraine headache. It is also indicated for the treatment of the signs and symptoms of mild to moderately severe, acute or chronic, musculoskeletal and soft tissue inflammation and acute gout.

CONTRAINDICATIONS
1. Hypersensitivity to naproxen.
2. Patients who have previously shown hypersensitivity reactions (e.g. nasal polyps, asthma, rhinitis, angioedema or urticaria) in response to aspirin or other NSAIDs. These reactions have the potential of being fatal.
3. Severe hepatic, renal, and cardiac failure.
4. During the last trimester of pregnancy.
5. Active or previous history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
6. Active or a history of upper gastrointestinal bleeding or perforation related to previous NSAIDs therapy.
7. Children under 2 years of age.

PREGNANCY AND LACTATION
Pregnancy
In view of the known effects of naproxen on the human foetal cardiovascular system (risk of closure of the ductus arteriosus), use in the last trimester of pregnancy is contraindicated. The onset of labour may be delayed and the duration increased with an increased bleeding tendency in both mother and child by naproxen. Therefore, naproxen should not be used during the first two trimesters of pregnancy or labour unless the potential benefit to the patient outweighs the potential risk to the foetus.

Labour and Delivery
Naproxen containing products are not recommended in labour and delivery because, through its prostaglandin synthesis inhibitory effect, naproxen may adversely affect foetal circulation and inhibit uterine contractions, with an increased bleeding tendency in both mother and child.

Lactation
Naproxen can appear in breast milk in very low concentrations. Because of the possible adverse effects of prostaglandin-inhibiting drugs on neonates, the use of naproxen in nursing mothers is not recommended.

ADVERSE EFFECTS
Gastrointestinal disorders:
Heartburn, nausea, vomiting, constipation, diarrhoea, flatulence, dyspepsia, abdominal discomfort and epigastric distress. More serious reactions which may occur are inflammation bleeding, which is sometimes fatal, particularly in older people, ulceration, perforation, and obstruction of the upper and lower gastrointestinal tract, melaena, haematemesis, stomatitis, exacerbation of ulcerative colitis and Crohn's disease, oesophagitis, gastritis and pancreatitis.

Immune system disorders:
Hypersensitivity reactions have been reported following treatment with NSAIDs in patients with, or without, a history of previous hypersensitivity reactions to NSAIDs. These may consist of (a) non-specific allergic reactions and anaphylaxis (b) respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea, or (c) assorted skin disorders, including rashes of various types, pruritus, urticaria, purpura, angiodema and, more rarely exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme).

Metabolic and nutrition disorders:
Hyperkalaemia.

Psychiatric disorders:
Insomnia, dream abnormalities, depression, confusion and hallucinations.

Nervous system disorders:
Convulsions, dizziness, headache, lightheadedness, drowsiness, paraesthesia, retrobulbar optic neuritis, inability to concentrate and cognitive dysfunction have been reported. Aseptic meningitis with symptoms such as stiff neck, headache, nausea, vomiting, fever or disorientation.

Eye Disorders:
Visual disturbances, corneal opacity, papillitis and papilloedema.

Ear and Labyrinth disorders:
Tinnitus, hearing disturbances including impairment and vertigo.

Cardiac Disorders:
Oedema, palpitations, hypertension, cardiac failure and congestive heart failure, have been reported. The use of coxibs and some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke).

Vascular disorders:
Hypertension, vasculitis.

Respiratory, thoracic and mediastinal disorders:
Dyspnoea, asthma, eosinophilic pneumonitis and pulmonary oedema.

Renal and urinary disorders:
Nephropathy and nephrotoxicity in various forms, including but not limited to glomerular nephritis, interstitial nephritis, nephrotic syndrome, haematuria, raised serum creatinine, renal disease, renal papillary necrosis and renal failure.

Hepatobiliary disorders:
Abnormal liver function tests, fatal hepatitis and jaundice.

Blood and lymphatic system disorders:
Granulocytopenia, thrombocytopenia, neutropenia, agranulocytosis, eosinophilia, leucopenia, aplastic anaemia and haemolytic anaemia.

Skin and subcutaneous tissue disorders:
Skin eruption, skin rashes including fixed drug eruption, itching (pruritus), urticaria, ecchymoses, purpura, sweating. Alopecia, erythema multiforme, bullous reactions Stevens Johnson syndrome, erythema nodosum, lichen planus, pustular reaction, SLE, epidermal necrolysis, very rarely toxic epidermal necrolysis, photosensitivity reactions (including cases in which skin resembles porphyria cutanea tarda “pseudoporphyria”) or epidermolysis bullosa-like reactions which may occur rarely, and angioneurotic oedema.

If skin fragility, blistering or other symptoms suggestive of pseudoporphyria occur, treatment should be discontinued and the patient monitored.

Musculoskeletal and connective tissue disorders:
Myalgia and muscle weakness.

Reproductive system and breast disorders:
Female infertility.

General disorders and administration site conditions:
Oedema, thirst, pyrexia, fatigue and malaise.

Investigations:
Abnormal liver function tests, raised serum creatinine.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Some patients may experience dizziness, drowsiness, vertigo, insomnia, fatigue and visual disturbances or depression with the use of naproxen sodium. If patients experience these or similar undesirable effects, they should not drive or operate machinery and exercise caution in carrying out activities that require alertness.

WARNINGS AND PRECAUTIONS
In all patients
Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms. Patients treated with NSAIDs long-term should undergo regular medical supervision to monitor for adverse events.

Sodium
275 mg tablet of naproxen contains approximately 25.06 mg of sodium. This should be considered in patients whose overall intake of sodium should be markedly restricted.

Fertility
The use of naproxen, as with any drug known to inhibit cyclooxygenase/prostaglandin synthesis, may impair fertility and is not recommended in women attempting to conceive. In women who have difficulty conceiving or are undergoing investigation of infertility, withdrawal of naproxen should be considered.

Elderly
The elderly and/or debilitated patients have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal. Prolonged use of NSAIDs in these patients is not recommended. Where prolonged therapy is required, patients should be reviewed regularly. In elderly patients the clearance is reduced. Use of lower end of the dosage range is recommended.

Antipyretic effects
The antipyretic and anti-inflammatory activities of naproxen may reduce fever and inflammation, thereby diminishing their utility as diagnostic signs.

Respiratory disorder
Caution is required if administered to patients suffering from or with a previous history of, bronchial asthma or allergic disease since NSAIDs have been reported to precipitate bronchospasm in such patients

Renal failure linked to reduced prostaglandin production
Caution should be observed in patients with conditions leading to a reduction in blood volume and/or renal blood flow as renal prostaglandins have a supportive role in the maintenance of renal perfusion. The administration of an NSAID may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure. Patients at greatest risk of this reaction are those with impaired renal function, cardiac impairment, liver dysfunction, those taking diuretics, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists and the elderly. Discontinuation of naproxen is usually followed by recovery to the pretreatment state. Naproxen should be used with great caution in such patients and the monitoring of serum creatinine and/or creatinine clearance is advised and patients should be adequately hydrated. A reduction in the daily dosage should be considered to avoid the possibility of excessive accumulation of naproxen metabolites in the patients. Renal function should also be assessed before and during naproxen therapy.

Use in patients with impaired renal function
Naproxen is eliminated to a large extent (95%) by urinary excretion via glomerular filtration, therefore it should be used with great caution in patients with significantly impaired renal function because naproxen is an inhibitor of prostaglandin synthesis. Naproxen is not recommended inpatients with baseline creatinine less than 30 ml/min because accumulation has been seen in such patients. Haemodialysis does not decrease the plasma concentration of naproxen because of the high degree of protein binding.

Renal Effects
There have been reports of impaired renal function, renal failure, acute interstitial nephritis, haematuria, proteinuria, renal papillary necrosis and occasionally nephrotic syndrome associated with naproxen.

Use in patients with impaired liver function
Chronic alcoholic liver disease and probably other forms of cirrhosis reduce the total plasma concentration of naproxen, but the plasma concentration of unbound naproxen is increased. It is prudent to use the lowest effective dose. As with other NSAIDs, elevations of one or more liver function tests may occur. Hepatic abnormalities may be the result of hypersensitivity rather than direct toxicity. Severe hepatic reactions, including jaundice and hepatitis (some cases of hepatitis have been fatal) have been reported with this drug as with other NSAIDs. Cross reactivity has been reported.

Use in patients with cardiovascular impairment
Caution should be exercised in patients with a history of hypertension and/or heart failure as fluid retention and oedema have been reported in association with NSAID therapy. Although sodium retention has not been reported in metabolic studies, it is possible that patients with questionable or compromised cardiac function may be at a greater risk when taking naproxen. Peripheral oedema has been observed in some patients taking naproxen or other NSAIDs.

SLE and mixed connective tissue disease
In patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders there may be an increased risk of aseptic meningitis.

Haematological
Patients who have coagulation disorders or are receiving drug therapy that interferes with haemostasis should be carefully observed if naproxen-containing products are administered. Patients at high risk of bleeding or those on full anti-coagulation therapies (e.g. dicoumarol derivatives) may be at increased risk of bleeding if given naproxen-containing products concurrently. Naproxen decreases platelet aggression and prolongs bleeding time. This effect should be kept in mind when bleeding times are determined.

Anaphylactic (anaphylactoid) reactions
Hypersensitivity reactions may occur in susceptible individuals. Anaphylactic (anaphylactoid) reactions may occur both in patients with and without a history of hypersensitivity or exposure to aspirin, other NSAIDs or naproxen-containing products. They may also occur in individuals with a history of angio-oedema, bronchospastic reactivity (e.g. asthma), rhinitis and nasal polyps. Anaphylactoid reactions, like anaphylaxis, may have a fatal outcome. Bronchospasm may be precipitated in patients suffering from, or with a history of asthma or allerfic disease or aspirin sensitivity.

Steroids
If steroid dosage is reduced or eliminated during therapy, the steroid dosage should be reduced slowly and the patients must be observed closely for any evidence of adverse effects, including adrenal insufficiency and exacerbation of symptoms of arthritis.

Combination with other NSAIDs
The combination of naproxen-containing products and other NSAIDs, including cyclooxygenase-2 selective inhibitors, should be avoided, because of the cumulative risks of inducing serious NSAID-related adverse events.

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

Cardiovascular and cerebrovascular events
Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy. The use of coxibs and some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). Although data suggest that the use of naproxen (1000 mg daily) may be associated with a lower risk, some risk cannot be excluded. Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with naproxen after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, and smoking).