MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

PACKAGE INSERTS FOR HUMAN MEDICINES STANDARDISED TEXTS

This guideline is intended to provide recommendations to applicants wishing to submit applications for the registration of medicines. It represents the Medicines Control Council's current thinking on the safety, quality and efficacy of medicines. It is not intended as an exclusive approach. Council reserves the right to request any additional information to establish the safety, quality and efficacy of a medicine in keeping with the knowledge current at the time of evaluation. Alternative approaches may be used but these should be scientifically and technically justified. The MCC is committed to ensure that all registered medicines will be of the required quality, safety and efficacy. It is important that applicants adhere to the administrative requirements to avoid delays in the processing and evaluation of applications.

Guidelines and application forms are available from the office of the Registrar of Medicines and the website.

Version 1: Removal of section 12 from the General Information guideline and inclusion in this guideline, with amendment of previous section 12.9 (Ace-inhibitors); Inclusion in this guideline of previous Communications to Industry re package insert texts, with amendment of Paracetamol-containing products.		November 2009
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Please read together with Notice R. 870 in Government Gazette No. 37032 of 15 November 2013 for the amendments to regulations 8, 9 and 10

REGISTRAR OF MEDICINES

Not updated in this version

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PACKAGE INSERT STANDARDISED TEXTS

1 INTRODUCTION

This guideline is relevant only to human medicines including biological and complementary medicines.

Refer also to the General Information guideline for PART 1C Labelling, the guideline ***"Package insert amendments concerning urgent safety restrictions: Urgent safety restriction notice (USRN)"***, the guideline "***Package Inserts for Human Medicines"***, and Regulation 9 of The Medicines and Related Substances Act, 1965 (Act 101 of 1965).

2 STANDARDISED PACKAGE INSERT TEXT - WARNINGS, SAFETY INFORMATION, OTHER

In addition to the warnings required by Regulations 8, 9 and 10 of the Act, the following warnings and other information should be included in the package insert, unless the applicant can provide convincing evidence to the contrary. The wording need not be identical.

2.1 ~~ACE-INHIBITORS~~

~~It is recommended that the package inserts for ACEIs include the following information:~~

~~2.1.1 Under Contra-indications~~

~~"Pregnancy and lactation (See 'Warnings' and 'Pregnancy and Lactation').~~

~~2.1.2 Under Warnings~~

~~"Should a woman become pregnant while receiving [PROPRIETARY NAME], the treatment should be stopped promptly and switched to a different class of medicine (See 'Contraindications' and 'Pregnancy and Lactation')".~~

~~2.1.3 Under Pregnancy and Lactation~~

~~"[PROPRIETARY NAME] passes through the placenta and can be presumed to cause disturbance in foetal blood pressure regulatory mechanisms. Oligohydramnios as well as hypotension, oliguria and anuria in newborns, have been reported after administration of [PROPRIETARY NAME] in the second and third trimester. Cases of defective skull ossification have been observed. Prematurity and low birth mass can occur. In addition, use of [PROPRIETARY NAME] during the first trimester of pregnancy has been associated with an increased risk of birth defects, in particular of the cardiovascular and the central nervous system. (See 'Contraindications' and 'Warnings')."~~

2.1 ACE-INHIBITORS AND ANGIOTENSIN RECEPTOR BLOCKERS (ARBs)

The following information should be included in the package inserts of Angiotensin converting enzyme (ACE) inhibitors and Angiotensin Receptor Blockers (ARBs):

2.1.1 Under CONTRA-INDICATIONS:

- Hypers~~S~~ensitivity to any of the ~~components~~ ingredients of [PROPRIETARY NAME]

- 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).
- ~~Moderate to s~~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. (see INTERACTIONS)
- Porphyria (or motivate if not contra-indicated)
- ~~Thiazide diuretics in (fixed dose) combination with [PROPRIETARY NAME] should not be given to patients with Addison's disease. This therapy is also contraindicated in patients with severe renal impairment or anuria, and in patients who show hypersensitivity to other sulphonamide-derived medicines.~~
- Lithium therapy: Concomitant administration with [PROPRIETARY NAME] may lead to toxic blood concentrations of lithium. (see INTERACTIONS)
- Pregnancy and lactation (see PREGNANCY AND LACTATION).
- The concomitant use of [PROPRIETARY NAME] with aliskiren-containing products is contraindicated. (see WARNINGS & SPECIAL PRECAUTIONS AND INTERACTIONS)

2.1.2 Under WARNINGS AND SPECIAL PRECAUTIONS

Should a woman become pregnant while receiving [PROPRIETARY NAME], the treatment should be stopped promptly and switched to a different class of antihypertensive medicine (See CONTRAINDICATIONS and PREGNANCY AND LACTATION).

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 [PROPRIETARY NAME] and aliskiren is therefore contraindicated (see CONTRAINDICATIONS).

[PROPRIETARY NAME] should not be used concomitantly with aliskiren. (see CONTRAINDICATIONS).

2.1.3 Under INTERACTIONS

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 aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (see CONTRAINDICATIONS, WARNINGS AND SPECIAL PRECAUTIONS).

2.1.4 Under PREGNANCY AND LACTATION

(i) The following information should be included in the package inserts of ACE inhibitors:

The use of [PROPRIETARY NAME] is contraindicated during pregnancy. Pregnant women should be informed of the potential hazards to the foetus and must not take [PROPRIETARY NAME] during pregnancy (see CONTRA-INDICATIONS). Patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with [PROPRIETARY NAME] should be stopped immediately and if appropriate, alternative therapy should be started.

Foetal exposure to ACE inhibitors during the first trimester of pregnancy has been reported to be associated with an increased risk of malformations of the cardiovascular (atrial and/or ventricular septal defect, pulmonic stenosis, patent ductus arteriosus) and central nervous system (microcephaly spins bifida) and of kidney malformations.

[PROPRIETARY NAME] passes through the placenta and can be presumed to cause disturbance in foetal blood pressure regulatory mechanisms.

Oligohydramnios as well as hypotension, oliguria and anuria in new-borns, have been reported after administration of [PROPRIETARY NAME] during the second and third trimester. Cases of defective skull ossification have been observed. Prematurity and low birth mass can occur (see CONTRA-INDICATIONS).

(ii) The following information should be included in the package inserts of Angiotensin Receptor Blockers (ARBs):

Safety in pregnancy and lactation has not been established (see CONTRA-INDICATIONS). When pregnancy is planned or confirmed [PROPRIETARY NAME] should be discontinued.

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

Women of childbearing age should ensure effective contraception

2.2 ANTIBIOTICS FOR THE TREATMENT OF BETA-HAEMOLYTIC STREPTOCOCCAL INFECTIONS

The following statement should be included under the heading, “DOSAGE AND DIRECTIONS FOR USE:”

“In the treatment of beta-haemolytic streptococcal infections, a therapeutic dose should be administered for at least 10 days.”

2.3 ALL ANTIRETROVIRAL MEDICINES (ARVs)

See also Nucleoside/Nucleotide Reverse Transcriptase Inhibitors

Warnings and Special Precautions

Lipodystrophy and metabolic abnormalities

Combination antiretroviral therapy has been associated with the redistribution/accumulation of body fat, including central obesity, dorso-cervical fat, enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and elevated serum lipid and glucose levels in HIV patients.

Clinical examination should include evaluation for physical signs of fat redistribution. Patients with evidence of lipodystrophy should have a thorough cardiovascular risk assessment.

Immune Reconstitution Inflammatory Syndrome

Immune reconstitution inflammatory syndrome (IRIS) is an immunopathological response resulting from the rapid restoration of pathogen-specific immune responses to pre-existing antigens combined with immune dysregulation, which occurs shortly after starting combination Anti-Retroviral Therapy (cART). Typically such reaction presents by paradoxical deterioration of opportunistic infections being treated or with unmasking of an asymptomatic opportunistic disease, often with an atypical inflammatory presentation. IRIS usually develops within the first three months of initiation of ART and occurs more commonly in patients with low CD4 counts. Common examples of IRIS reactions to opportunistic diseases are tuberculosis, cytomegalovirus retinitis, and cryptococcal meningitis.

Appropriate treatment of the opportunistic disease should be instituted or continued and ART continued. Inflammatory manifestations generally subside after a few weeks. Severe cases may respond to glucocorticoids, but there is only limited evidence for this in patients with tuberculosis IRIS. Autoimmune disorders (such as Graves' disease) have also been reported as IRIS reactions; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Osteonecrosis

Although the aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported, particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy (cART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Opportunistic infections

Patients receiving [Proprietary Name] should be advised that they may continue to develop opportunistic infections and other complications of HIV infection, and therefore they should remain under close observation by healthcare professionals experienced in the treatment of patients with associated HIV disease. Regular monitoring of viral load and CD4 counts needs to be done.

The risk of HIV transmission to others

Patients should be advised that current antiretroviral therapy, including [Proprietary Name], does not prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be employed.

2.4 BETA-LACTAM ANTIBIOTICS

The following statement should be included in the package inserts of all beta-lactam and fluoroquinolone antibiotics containing an indication or claim for *Pseudomonas aeruginosa* infections.

Indications:

In the treatment of infections caused by *Pseudomonas aeruginosa*, an aminoglycoside should be administered concomitantly."

2.5 ANTIHISTAMINES (OLD GENERATION) GENERAL DROWSINESS WARNING

"This medicine may lead to drowsiness and impaired concentration that may be aggravated by the simultaneous intake of alcohol or other central nervous system depressants. Patients should be advised, particularly at the initiation of therapy, against taking charge of vehicles or machinery or performing potentially hazardous tasks where loss of concentration could lead to accidents."

2.6 ANTIHISTAMINES (NEW GENERATION) GENERAL DROWSINESS WARNING

"This medicine lacks significant sedative effects."

2.7 WARNING ON HYPERGLYCAEMIA AND DIABETES MELLITUS WITH ATYPICAL ANTIPSYCHOTIC AGENTS

The package inserts of atypical antipsychotic agents should include a standard safety warning relating to hyperglycaemia as reflected below:

WARNINGS

Hyperglycaemia and Diabetes Mellitus

Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with [PROPRIETARY NAME].

Patients with an established diagnosis of diabetes mellitus who are started on [PROPRIETARY NAME] should be monitored regularly for worsening of glucose control.

Patients with risk factors for diabetes mellitus (e.g. obesity, family history of diabetes) who are starting treatment with [PROPRIETARY NAME] should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycaemia during treatment with [PROPRIETARY NAME] should undergo fasting blood glucose testing.

In some cases, hyperglycaemia has resolved when [PROPRIETARY NAME] was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug."

2.8 BENZALKONIUM CHLORIDE-PRESERVED OPHTHALMOLOGICAL PREPARATIONS

The concentration of benzalkonium chloride should not exceed 0,01 % and should not be used in preparations intended for soft contact lens solutions.

The following warnings should be included in the package insert:

"As the possibility of adverse effects on the corneal permeability, and the danger of disruption of the corneal epithelium with prolonged or repeated usage of benzalkonium chloride preserved ophthalmological preparations, cannot be excluded, regular ophthalmological examination is required. Caution should be exercised in the use of benzalkonium chloride preserved topical medication over an extended period in patients with extensive ocular surface disease."

2.9 BENZODIAZEPINE OR BENZODIAZEPINE-LIKE COMPOUNDS

Product name to be inserted in [ ]

2.9.1 Indications

"[ ] is only indicated when the disorder is severe, disabling or when the individual is subject to extreme stress."

2.9.2 Dosage and directions for use

"Treatment should be started with the lowest recommended dose. The maximum dose should not be exceeded."

For products with anxiety approved as indication:

"Treatment should be as short as possible. The patient should be assessed regularly and the need for continued treatment should be re-evaluated especially when the patient is symptom-free. The overall duration of treatment, generally, should not be more than 8 to 12 weeks, including a tapering off process. In certain cases extension beyond the maximum treatment period may be necessary. If so, it should not take place without re-evaluation of the patient's status."

For products with insomnia approved as an indication:

Treatment should be as short as possible. Generally, the duration of treatment varies from a few days to two weeks, with a maximum of four weeks including the tapering-off process. In certain cases, extension beyond the maximum treatment period may be necessary. If so, it should not take place without re-evaluation of the patient's status."

2.9.3 Side effects and special precautions

"[ ] is not recommended for the primary treatment of psychotic illness. [ ] should not be used alone to treat depression, or anxiety with depression, as suicide may be precipitated in such patients. [ ] should be used with extreme caution in patients with a history of alcohol or drug abuse."

Dependence:

"There is a potential for abuse and the development of physical and psychological dependence, especially with prolonged use and high doses. The risk of dependence is also greater in patients with a history of alcohol or drug abuse. Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. These may consist of headaches, muscle pain, extreme anxiety, tension, restlessness, confusion and irritability."

"In severe cases, the following symptoms may occur: de-realisation, depersonalisation, hyperacusis, numbness and tingling of extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures."

Rebound effects:

"A transient syndrome, which may occur in withdrawal of treatment, whereby the symptoms that led to treatment with [ ] recur in an enhanced form. It may be accompanied by other reactions including mood changes, anxiety and restlessness. Since the risk of withdrawal or rebound phenomena, is greater after abrupt discontinuation of treatment, it is recommended that the dosage be decreased gradually."

Duration of treatment:

"The duration of treatment should be as short as possible (see Dosage), but should not exceed four weeks for insomnia and eight to twelve weeks in case of anxiety, (**) including the tapering-off process.

Extension beyond these periods should not take place without re-evaluation of the patient. It may be useful to inform the patient, when treatment is started, that it will be of limited duration, and to explain precisely how the dosage will be progressively decreased. Moreover, it is important that the patient is aware of the possibility of rebound phenomena, thereby minimising anxiety over such symptoms should they occur while the product is being discontinued."

"(**) Note that the duration should be adapted according to approved indications for each individual product."

2.10 BENZODIAZEPINE

Unless the applicant can provide convincing evidence to the contrary, package inserts for benzodiazepine should contain the following, although the wording need not be identical:

2.10.1 Side-effects and special precautions

"The side-effects most frequently encountered are drowsiness and over-sedation. Drowsiness is more common in elderly and debilitated patients, and in those receiving high doses. Less common are depression of mood and affect, disorientation or confusion, lethargy, ataxia, constipation, nausea, diarrhoea and changes in libido."

"Paradoxical reactions such as acute hyper-excitability with rage may occur. If these occur, the medicine should be discontinued."

"There is a potential for abuse. Withdrawal symptoms (including convulsions) have occurred following abrupt cessation, especially in patients who have received large doses for prolonged periods."

"Injections: Respiratory depression due to a depressant effect on the respiratory centre and cardiovascular collapse may occur following intravenous and intramuscular administration."

Special Precautions: "Particular caution should be exercised with the elderly and debilitated - who are at particular risk of over-sedation, respiratory depression and ataxia. (The initial oral dosage should be reduced in these patients)."

"Caution should be exercised in the following patients:

- patients suffering from impairment of renal or hepatic function;
- patients suffering from anxiety accompanied by an underlying depressive disorder;
- patients receiving barbiturates or other central nervous system depressants. There is an additive risk of central nervous system depression when these medicines are taken together;
- patients should be cautioned regarding the additive effect of alcohol."

"The medicine should be used judiciously during pregnancy and preferably avoided. During labour it crosses the placenta and may cause the "floppy-infant" syndrome characterised by central respiratory depression, hypothermia and poor sucking. It should not be administered to lactating mothers."

"Patients should be advised, particularly at the initiation of therapy, not to drive a motor vehicle or operate dangerous machinery or perform potentially hazardous tasks where impaired decision making could lead to accidents."

2.10.2 Overdosage

"Manifestations of overdosage include somnolence, confusion, coma, respiratory and cardiovascular depression and hypotension."

2.11 BETA-BLOCKING AGENTS

Unless the applicant can provide convincing evidence to the contrary, package inserts for beta-blocking agents should contain the following, although the wording need not be identical:

2.11.1 Side effects and special precautions

"Bronchoconstriction may occur in patients suffering from asthma, bronchitis and other chronic pulmonary diseases. Congestive cardiac failure and marked bradycardia may also manifest. A variety of neuropsychiatric disorders, ranging from vague fatigue and nightmares to overt psychosis, have been observed."

"The following may occur: exacerbation of peripheral vascular disease, or the development of Raynaud's phenomenon (due to unopposed arteriolar alpha-sympathetic activation), sexual impotence, hypoglycaemia, skeletal muscle weakness and gastro-intestinal disturbances. Severe peripheral vascular disease and even peripheral gangrene may be precipitated. Adverse reactions are more common in patients with renal decompensation, and in patients who receive the drug intravenously."

"It is dangerous to administer this medicine concomitantly with the following medicines: hypoglycaemic agents, phenothiazines and various antiarrhythmic agents. Such drug-drug interactions can have life-threatening consequences."

"SPECIAL NOTE: - digitalisation of patients receiving long-term beta-blocker therapy may be necessary if congestive cardiac failure is likely to develop. This combination can be considered despite the potentiation of the negative chronotropic effect of the two medicines. Careful control of dosages, and of the individual patient's response (and notably pulse rate), is essential in this situation."

"Abrupt discontinuation of therapy may cause exacerbation of angina pectoris in patients suffering from ischaemic heart disease. Discontinuation of therapy should be gradual, and patients should be advised to limit the extent of their physical activity during the period that the medicine is being discontinued."

"Administration to pregnant mothers shortly before giving birth or during labour may result in the newborn infants being born hypotonic, collapsed and hypoglycaemic."

"Patients with phaeochromocytoma usually require treatment with an alpha-adrenergic blocker."

2.11.2 Contra-Indications

"Particular caution should be exercised with patients suffering from the following: asthma, bronchitis, chronic respiratory diseases, second and third degree heart block and bradycardia (less than 50 beats per minute), peripheral vascular diseases and Raynaud's phenomenon. The normal dose should be reduced in elderly patients, or in patients suffering from renal dysfunction. In the peri-operative period, it is generally unwise to reduce the dosage to which the patient is accustomed, as there may be danger of aggravation of angina pectoris or hypertension. A patient's normal tachycardic response to hypovolaemia or blood loss may be obscured during or after surgery. Particular caution should be taken in this regard."

2.11.3 Known symptoms of overdosage and particulars of its treatment:

"Overdosage may produce bradycardia and severe hypotension. Bronchospasm and heart failure may be produced in certain individuals. Cases of mild overdose should be observed for at least four hours, as apnoea and cardiovascular collapse may appear suddenly. Gastric lavage should be performed within four hours of suspected overdose. Repeated activated charcoal is necessary in severe overdose."

"Atropine may be used to treat severe bradycardia. If the response is inadequate, glucagon may be given intravenously. Alternatively, dobutamine or isoprenaline, may be required to reverse beta-blockade. Intravenous cardiac pacing may be required for severe bradycardia. Bronchospasm should be treated with IV aminophylline or inhaled, or IV beta-agonist, e.g. salbutamol."

2.12 BETA-BLOCKER AND CLONIDINE

The following warnings should be included in all beta-blocker and clonidine package inserts.

"Caution should be exercised when transferring a patient from clonidine. The withdrawal of clonidine may result in the release of large amounts of catecholamines that may give rise to a hypertensive crisis. If beta-blockers are administered in these circumstances, the unopposed alpha receptor stimulation may potentiate this effect."

"If a beta-blocker and clonidine are given concurrently, the clonidine should not be discontinued until several days after the withdrawal of the beta-blocker, as severe rebound hypertension may occur."

2.13 BETA-2 AGONISTS

2.13.1 Indications

"Treatment of reversible airway obstruction in asthma, chronic bronchitis and emphysema, and prevention of bronchospasm in exercised-induced asthma."

2.13.2 Side effects and special precautions

"Hypokalaemia may occur. Overdosage may cause cardiac effects. High doses may increase the risk of serious side effects, including cardiac dysrhythmias. This risk is further aggravated if the drug is administered concomitantly with other medicines that cause hypokalaemia and cardiac dysrhythmias, or in the presence of hypoxia and acidosis. The maximum dose should not be exceeded."

2.13.3 Dosage and directions for use

"Do not exceed the recommended dose."

2.14 BISMUTH-CONTAINING MEDICINES

The package inserts for bismuth-containing preparations should include a warning regarding the possibility of neurotoxicity with prolonged or excessive use.

2.15 BISPHOSPHONATE-CONTAINING MEDICINES

The following information should be included in the package inserts of bisphopsphonate-containing medicines

2.15.1 Under WARNINGS AND SPECIAL PRECAUTIONS:

Atypical fractures of the femur

Atypical, low energy fractures of the subtrochanteric and proximal femoral shaft have been reported with long-term use (usually longer than 3 years) in bisphosphonate-treated patients. Some were stress fractures (also reported as insufficiency fractures) occurring in the absence of apparent trauma. Some patients experienced prodromal pain in the affected area, often associated with

imaging features of stress fracture, weeks to months before a fracture occurred. Approximately one third of these fractures were bilateral; therefore the contralateral femur should be examined in patients who have sustained a femoral shaft stress fracture and receive appropriate orthopaedic care. Bisphosphonate treatment should be stopped in patients with stress fractures and they should receive appropriate orthopaedic care.

Osteonecrosis of the jaw

Osteonecrosis of the jaw generally associated with tooth extraction and/or local infection (including osteomyelitis) has been reported in patients with cancer receiving treatment regimens including primarily intravenous administered bisphosphonates. Many of these were receiving chemotherapy and corticosteroids. Osteonecrosis of the jaw has also been reported in patients with osteoporosis receiving oral bisphosphonates, such as [PROPRIETARY NAME].

A dental examination with appropriate preventative dentistry should be considered prior to treatment with bisphosphonates, such as [PROPRIETARY NAME] in patients with concomitant risk factors (e.g. cancer, chemotherapy, radiotherapy, corticosteroids, poor oral hygiene).

While on treatment, these patients should avoid invasive dental procedures if possible. For patients who develop osteonecrosis of the jaw while on bisphosphonate therapy, such as [PROPRIETARY NAME], dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of osteonecrosis of the jaw.

Clinical judgment of the treating doctor should guide the management plan of each patient based on an individual benefit/risk assessment.

2.16 CLOFIBRATE

Package inserts for all clofibrate-containing medicines should reflect the following statement:

2.16.1 Indications

"Before starting treatment with clofibrate, attempts should be made to control serum lipids with appropriate dietary regimens, e.g. weight loss in obese patients, control over diabetes mellitus. If, after considering the possible benefits in relation to the risks, it is decided to institute clofibrate therapy, then it should be indicated in the treatment of types II(B), III, IV and V hyperlipoproteinaemias
(Frederickson and Levy Classification)."

FREDERICKSON TYPE	LIPOPROTEIN ELEVATION	MAJOR ELEVATION	LIPID
I (very rare)	chylomicra	Triglycerides	
II (a)	LDL	Cholesterol	
II (b)	pre- (VLDL & LDL)	Cholesterol Triglycerides	&
III (rare)	Abnormal (LDL)	Cholesterol Triglycerides	&
IV	Pre (VLDL)	Cholesterol Triglycerides	&
V (rare)	Chylomicra & pre (VLDL)	Cholesterol Triglycerides	&

"It has not been established whether the drug-induced lowering of serum cholesterol or lipid levels has detrimental, beneficial or no effects, on morbidity or mortality, due to atherosclerosis or coronary heart disease. Clofibrate therapy should be discontinued if a significant lowering in serum lipids is not obtained."

2.16.2 Side effects and special precautions

"Due to its action on cholesterol metabolism, clofibrate may increase the lithogenicity of bile and, thereby, cause an increased frequency of gallstones. A possible association between treatment with clofibrate and gastro-intestinal malignancies exists."

2.17 CODEINE WARNING

The following warning should appear on the immediate container label, the outer label (if applicable) and the package insert of all CODEINE-containing products.

"Exceeding the prescribed dose, together with prolonged and continuous use of this medication, may lead to dependency and addiction."

2.18 CONTRAST MEDIA - WATER SOLUBLE - BOXED WARNING

"Fatal reactions have been associated with the administration of water-soluble contrast media. It is, therefore, of utmost importance that a course of action is carefully planned, in advance, for the immediate treatment of serious reactions, and that adequate and appropriate facilities and personnel be readily available in case of a severe reaction. Patients should be observed for a possible severe reaction, during, and for at least 30 to 60 minutes after, administration of [PROPRIETARY NAME]. Patients with known or suspected hypersensitivity to iodated contrast media should be closely observed."

2.19 POTENT TOPICAL CORTICOSTEROIDS

The following warning should be included in all potent topical corticosteroid package inserts:

"Potent topical corticosteroid preparations, such as (name), should not be applied to any skin crease areas."

2.20 CORTICOSTEROIDS PRODUCTS FOR TOPICAL USE

Package insert for all topical corticosteroid should reflect the following:

Contra-indications:

"Corticosteroids have been shown to be teratogenic in animals following dermal application. As these agents are absorbed percutaneously, teratogenicity following topical application cannot be excluded. Therefore, [Proprietary Name] should not be used during pregnancy."

2.21 CO-TRIMOXAZOLE

All package inserts of products containing co-trimoxazole, or long-acting sulphonamides, should include a warning with regard to the occurrence of erythema multiforme, toxic dermal necrolysis and allergic vasculitis.

2.22 COX-2 INHIBITORS

The following information must be included in the package inserts of COX-2 inhibitors:

2.22.1 Contraindications

- Heart failure, established ischaemic heart disease and/or cerebrovascular disease (stroke) and peripheral arterial disease
- Perioperative analgesia in the setting of coronary artery bypass surgery (CABG)
- For sulphonamide containing moieties: Known sulphonamide hypersensitivity

2.22.2 Warnings and Special Precautions

- A boxed warning:

> [PROPRIETARY NAME] may predispose to cardiovascular events, gastrointestinal events, or cutaneous reactions which may be fatal.

- Serious skin reactions, which can be fatal, may occur.
- There appears to be a higher risk for cardiovascular events with higher doses and longer duration of treatment.
- Caution is advised when [PROPRIETARY NAME] is prescribed to patients with cardiovascular risk factors e.g. hypertension, diabetes, smoking and hypercholesterolaemia.
- Because of its lack of platelet effects, [PROPRIETARY NAME] is not a substitute for aspirin for cardiovascular prophylaxis.
- Due to inhibition of prostaglandin synthesis, fluid retention and oedema have been observed in patients taking [PROPRIETARY NAME], therefore [PROPRIETARY NAME] should be used with caution in patients with compromised cardiac function and other conditions predisposing to, or worsened by, fluid retention. Patients with pre-existing congestive heart failure or hypertension should be closely monitored.

2.22.3 Interactions

- Because of its lack of platelet effects, [PROPRIETARY NAME] is not a substitute for aspirin for cardiovascular prophylaxis.
- There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious cardiovascular thrombotic events associated with [PROPRIETARY NAME].

2.22.4 Dosage and Directions for Use

- Use the lowest effective dose for the shortest possible duration of treatment.

2.22.5 Under Side Effects

- *Cardiac disorders:* peripheral oedema, dysrhythmia, palpitations, tachycardia, congestive cardiac failure, myocardial infarction, cardiovascular thrombotic events
- *Vascular disorders:* aggravated hypertension, hypertension
- *Nervous system disorders:* cerebrovascular incidents (strokes)

2.23 DISOPYRAMIDE

2.23.1 Side-effects and special precautions

"The administrations of disopyramide may precipitate cardiac failure when administered to patients with congestive failure who have been stabilised."

2.23.2 Contra-indications

"The administration of disopyramide is contra-indicated in patients with congestive cardiac failure, irrespective of whether the patient is digitalised, or not."

2.24 FLUOROQUINOLONE ANTIBIOTICS

Refer to Beta-lactam antibiotics.

2.25 GLIBENCLAMIDE and GLICLAZIDE: BOXED WARNING

"A reduction in dosage may be necessary in patients with renal dysfunction."

2.26 IODINE AND IODIDE-CONTAINING MEDICINES

Synthetic thyroid hormone preparations are exempted from the following requirements.

The following warning should appear on the LABELS as well as in the PACKAGE INSERTS of all medicines containing more than 0,60 mg iodine/ionic iodide per daily dose:

"Not to be used during pregnancy or lactation."

On the package inserts of ALL iodine-containing preparations, there should be a warning:

"Not to be used by persons who are allergic to iodine."

2.27 MALARIA PROPHYLAXIS IMPORTANT PATIENT INFORMATION

The following patient warnings should be included in all package inserts of products intended for malaria prophylaxis:

"Because no form of prophylaxis is fully effective, the prevention of mosquito bites should form the mainstay of malaria prophylaxis. The following preventative measures to prevent mosquito bites should be taken:

a) Endemic areas should preferably be visited during the dry season or in years when rainfall is low.

b) High-risk patients should avoid malaria areas altogether.

High-risk persons include:

- babies and young children less than 5 years of age;
- pregnant women;
- immuno-compromised individuals such as those on long-term steroids, cancer patients and those on chemotherapy, AIDS patients and those who have had their spleens removed.

c) Refrain from going outside between dusk and dawn when mosquitoes are most active.

d) Apply insect repellent to exposed skin and clothing.

e) Wear long sleeves and trousers at night.

f) Use mosquito nets, screens, coils or pads."

"Should the patient develop flu-like symptoms, the patient should inform the doctor that he has been to a malaria endemic area."

2.28 METOCLOPRAMIDE

This warning should appear on ALL package inserts:

"The use of metoclopramide during pregnancy is considered unsafe as teratogenicity has been demonstrated in animal studies."

2.29 METRONIDAZOLE

The following warning should be included in the package inserts of all products containing metronidazole:

"Pseudomembranous colitis has been reported following the use of metronidazole."

2.30 NON-STEROIDAL ANTI-INFLAMMATORY AGENTS

The following warning, regarding the use of non-steroidal anti-inflammatory drugs in pregnancy, should be included in all package inserts of non-steroidal anti-inflammatory agents:

"Regular use of non-steroidal anti-inflammatory drugs during the third trimester of pregnancy, may result in premature closure of the foetal ductus arteriosus *in utero*, and possibly, in persistent pulmonary hypertension of the new-born. The onset of labour may be delayed and its duration increased."

In addition to the above, the following special precaution should be included: "In view of the product's inherent potential to cause fluid retention, heart failure may be precipitated in some compromised patients."

2.31 ALL NON-SELECTIVE NSAIDs (INCLUDING ASPIRIN)

The following information should be included in the package inserts of non-selective NSAIDs (including aspirin):

2.31.1 Under Contraindications

- Heart failure
- For diclofenac: Heart failure, established ischaemic heart disease and/or cerebrovascular disease (stroke) and peripheral arterial disease
- History of gastrointestinal perforation, ulceration or bleeding (PUBs) related to previous NSAIDs, including [PROPRIETARY NAME].
- Active or history of recurrent ulcer/haemorrhage/perforations.

2.31.2 Under Warnings and Special Precautions

- Caution is required in patients with a history of hypertension and/or heart failure as fluid retention and oedema have been reported in association with [PROPRIETARY NAME] therapy. In view of the [PROPRIETARY NAME]'s inherent potential to cause fluid retention, heart failure may be precipitated in some compromised patients.
- Caution is required in patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) and should only be treated with diclofenac after careful consideration.
- Elderly: The elderly have an increased frequency of adverse reactions to NSAIDs including [PROPRIETARY NAME], especially gastrointestinal perforation, ulceration and bleeding (PUBs) which may be fatal.
- The risk of gastrointestinal perforation, ulceration or bleeding (PUBs) is higher with increasing doses of [PROPRIETARY NAME], in patients with a history of ulcers, and the elderly.
- When gastrointestinal bleeding or ulceration occurs in patients receiving [PROPRIETARY NAME], treatment with [PROPRIETARY NAME] should be stopped.
- [PROPRIETARY NAME] should be given with caution to patients with a history of gastrointestinal disease (e.g. ulcerative colitis, Crohn's disease, hiatus hernia, gastro-oesophageal reflux disease, angiodysplasia) as the condition may be exacerbated.
- Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolyis have been reported. [PROPRIETARY NAME] should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.
- Regular use of NSAIDs such as [PROPRIETARY NAME] during the third trimester of pregnancy, may result in premature closure of the foetal ductus arteriosus *in utero*, and possibly, in persistent pulmonary hypertension of the new-born. The onset of labour may be delayed and its duration increased.

2.31.3 Under Interactions

- NSAIDs: use of two or more NSAIDs concomitantly could result in an increase in side effects
- Corticosteroids: increased risk of gastrointestinal perforation, ulceration or bleeding (PUBs)
- Anti-coagulants: [PROPRIETARY NAME] may enhance the effects of anti-coagulants such as warfarin
- Anti-platelet medicines and selective serotonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding.

2.31.4 Under Dosage and Directions for Use

- Use the lowest effective dose for the shortest possible duration of treatment.

2.31.5 Under Side Effects

- Cardiac disorders: Oedema, hypertension and cardiac failure.
- Gastrointestinal system disorders: The most commonly observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or gastrointestinal bleeding, sometimes fatal. Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease, gastritis.
- Skin and subcutaneous tissue disorders: Bullous reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis.

2.32 NUCLEOSIDE/NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS

See also section 2.4 ALL ANTIRETROVIRAL MEDICINES (ARVs)

Warnings and Special Precautions

Lactic acidosis / hyperlactataemia

Use of [PROPRIETARY NAME] can result in potentially fatal lactic acidosis as a consequence of mitochondrial dysfunction.

Clinical features are non-specific, and include nausea, vomiting, abdominal pain, dyspnoea, fatigue and weight loss.

In patients with suspicious symptoms or biochemistry, measure the venous lactate level (normal < 2 mmol/ℓ) and the serum bicarbonate and respond as follows:

- Lactate 2-5 mmol/ℓ with minimum symptoms: switch to agents that are less likely to cause lactic acidosis.
- Lactate 5-10 mmol/ℓ with symptoms and/or with reduced standard bicarbonate: Stop NRTIs and change treatment option. Once lactate has settled, use medicines that are less likely to cause lactic acidosis. Exclude other causes, (e.g. sepsis, uraemia, diabetic ketoacidosis, thyrotoxicosis and hyperthyroidism.
- Lactate> 10 mmol/ℓ: STOP all therapy (80 % mortality).

The above lactate values may not be applicable to paediatric patients.

Caution should be exercised when administering [PROPRIETARY NAME] to patients with known risk factors for liver disease.

Treatment with [PROPRIETARY NAME] should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity.

Mitochondrial dysfunction

Nucleoside and nucleotide analogues have been demonstrated *in vitro* and *in vivo* to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in HIV negative infants exposed *in utero* and/or post-natally to nucleoside analogues. Apart from lactic acidosis/hyperlactataemia (see above) other manifestations of mitochondrial dysfunction include haematological disorders (anaemia, neutropenia), and peripheral neuropathy. Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behaviour). It is not known whether the neurological disorders are transient or permanent. Any foetus exposed *in utero* to nucleoside and nucleotide analogues, even HIV negative infants/children, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant sign and symptoms.

Pancreatitis

Pancreatitis has been observed in some patients receiving [PROPRIETARY NAME].

Pancreatitis must be considered whenever a patient develops abdominal pain, nausea, vomiting or elevated biochemical markers. Discontinue use of [PROPRIETARY NAME] until diagnosis of pancreatitis is excluded.

Patients with moderate to severe renal impairment

In patients with moderate to severe renal impairment, the terminal half-life of [PROPRIETARY NAME] is increased due to decreased clearance. The dose of [PROPRIETARY NAME] should therefore be adjusted* (see DOSAGE AND DIRECTION FOR USE). *[*not applicable to abacavir]*

Liver disease

Use of [PROPRIETARY NAME] can result in hepatomegaly due to non-alcoholic fatty liver disease (hepatic steatosis). The safety and efficacy of [PROPRIETARY NAME] has not been established in patients with significant underlying liver disorders/diseases. In case of concomitant antiviral therapy for hepatitis B or C, please also consult the relevant package inserts for these medicines.

Patients with pre-existing liver dysfunction including chronic active hepatitis have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored. If there is evidence of worsening liver disease in such patients, temporary or permanent discontinuation of treatment must be considered.

Patients with HIV and hepatitis B or C virus co-infection

Patients with chronic hepatitis B or C and treated with antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions.

Medical practitioners should refer to current HIV treatment guidelines for the optimal management of HIV infection in patients co-infected with hepatitis B virus (HBV).

In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant package inserts for these medicines.

Patients co-infected with HIV and HBV who discontinue [PROPRIETARY NAME]should be closely monitored with both clinical and laboratory follow-up after stopping treatment. In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation.

Only relevant to lamivudine, tenofovir and emtricitabine (FTC): Discontinuation of [PROPRIETARY NAME] therapy in patients co-infected with HIV and HBV may be associated with severe, acute exacerbations of hepatitis.

2.33 OESTROGEN-CONTAINING PRODUCTS

With the exclusion of oestrogen-containing oral contraceptives, all other oestrogen-containing medicines shall have package inserts bearing the following warnings:

"Not for use during pregnancy. Vaginal adenosis, and vaginal and cervical adenocarcinoma, has been noted in post-pubertal girls whose mothers were treated for threatened abortion with large doses of stilboestrol, or related oestrogenic substances, during their pregnancies."

"An increased incidence of endometrial uterine carcinoma, related to the continuous use of oestrogens in the post-menopausal period, has been reported."

Products intended solely for post-menopausal use may have in their package inserts, instead of the aforementioned warning, the warning:

"Not for use during pregnancy."

All combination oral contraceptive products containing oestrogen shall have package inserts reflecting:

Side effects and special precautions

"Oral contraceptive failure may occur with concomitant antibiotic therapy. For maximal protection, additional non-hormonal contraception is recommended for the duration of antibiotic therapy and for seven days thereafter. Those on long-term antibiotic therapy need only take extra precautions for the first two weeks of antibiotic therapy. Spotting and breakthrough bleeding are possible signs of diminished contraceptive effectiveness."

2.34 OXYPHENBUTAZONE

The indications and period of use for oxyphenbutazone preparations should be restricted to "acute exacerbations of ankylosing spondylitis" and a maximum period of use of 7 days.

Warnings (to be in prominent type and boxed) - the following should be included:

"Because of potentially serious and occasionally fatal adverse effects, use should be restricted to a maximum of 7 days and the maximum recommended dosage should not be exceeded. Caution against repeated short-term use is advised due to the possible danger of sensitisation. Haematological disorders are potentially fatal. For parenteral dosage forms, the dosage should be limited to a maximum of 600 mg per day."

2.35 PARACETAMOL-CONTAINING PRODUCTS

The following information relating to overdosage should be included in the package inserts for all paracetamol-containing products:

2.35.1 Warnings

(i) the following statement, boxed:

This product contains paracetamol which may be fatal in overdose. In the event of overdosage or suspected overdose and notwithstanding the fact that the person may be asymptomatic, the nearest doctor, hospital or Poison Centre must be contacted immediately.

(ii) Dosages in excess of those recommended may cause severe liver damage.

Note: This does not exclude the inclusion of further information. Other information required under 'Warnings' is not addressed here.

2.35.2 Dosage and Directions for Use:

In bold: "DO NOT EXCEED THE RECOMMENDED DOSE."

2.35.3 Known Symptoms of Overdosage and Particulars of its Treatment

Because [PROPRIETARY NAME] is an extended release paracetamol formulation, absorption will be prolonged in overdose. [For all modified release formulations.]

Prompt treatment is essential. In the event of an overdosage, consult a doctor immediately, or take the person directly to a hospital. A delay in starting treatment may mean that antidote is given too late to be effective. Evidence of liver damage is often delayed until after the time for effective treatment has lapsed.

Susceptibility to paracetamol toxicity is increased in patients who have taken repeated high doses (greater than 5 -10 g/day) of paracetamol for several days, in chronic alcoholism, chronic liver disease, AIDS, malnutrition, and with the use of drugs that induce liver microsomal oxidation such as barbiturates, isoniazid, rifampicin, phenytoin and carbamazepine.

Symptoms of paracetamol overdosage in the first 24 hours include pallor, nausea, vomiting, anorexia and possibly abdominal pain. Mild symptoms during the first two days of acute poisoning, do not reflect the potential seriousness of the overdosage.

Liver damage may become apparent 12 to 48 hours, or later after ingestion, initially by elevation of the serum transaminase and lactic dehydrogenase activity, increased serum bilirubin concentration and prolongation of the prothrombin time. Liver damage may lead to encephalopathy, coma and death.

Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage. Abnormalities of glucose metabolism and metabolic acidosis may occur. Cardiac arrhythmias have been reported.

Treatment for paracetamol overdosage:

Although evidence is limited it is recommended that any adult person who has ingested 5 - 10 grams or more of paracetamol (or a child who has had more than 140 mg/kg) within the preceding four hours, should have the stomach emptied by lavage (emesis may be adequate for children) and a single dose of 50 g activated charcoal given via the lavage tube. Ingestion of amounts of paracetamol smaller than this may require treatment in patients susceptible to paracetamol poisoning (see above). In patients who are stuperose or comatose endotracheal intubation should precede gastric lavage in order to avoid aspiration.

N-acetylcysteine should be administered to all cases of suspected overdose as soon as possible preferably within eight hours of overdosage, although treatment up to 36 hours after ingestion may still be of benefit, especially if more than 150 mg/kg of paracetamol was taken. An initial dose of 150 mg/kg N-acetylcysteine in 200 ml dextrose injection given **intravenously** over 15 minutes, followed by an infusion of 50 mg/kg in 500 ml dextrose injection over the next four hours, and then 100 mg/kg in 1 000 ml dextrose injection over the next sixteen hours. **The volume of intravenous fluid should be modified for children**.

Although the oral formulation is not the treatment of choice, 140 mg/kg dissolved in water may be administered initially, followed by 70 mg/kg every four hours for seventeen doses.

A plasma paracetamol level should be determined four hours after ingestion in all cases of suspected overdosage. Levels done before four hours may be misleading. Patients at risk of liver damage, and hence requiring continued treatment with N-acetylcysteine, can be identified according to their 4-hour plasma paracetamol level. The plasma paracetamol level can be plotted against time since ingestion in the nomogram below. The nomogram should be used only in relation to a single acute ingestion.

Those whose plasma paracetamol levels are above the “normal treatment line”, should continue N-acetylcysteine treatment with 100 mg/kg IV over sixteen hours repeatedly until recovery. Patients with increased susceptibility to liver damage as identified above, should continue treatment if concentrations are above the “high risk treatment line”. Prothrombin index correlates best with survival.

For overdose with an extended/modified release preparation the value of the nomogram is unknown. As there is no information on the plasma levels of paracetamol after an overdose of extended/modified release paracetamol preparations, all patients with suspected or known overdose with such preparations should receive N-acetylcysteine. Because of lack of data for extended/modified release formulations, a level below the “treatment line” of the nomogram may not exclude the possibility of toxicity.

Monitor all patients with significant ingestions for at least ninety six hours.

Note: Applicant to include nomogram (semi-logarithmic plot) for paracetamol plasma concentration against time after ingestion and to quote the appropriate source reference.

2.36 POTASSIUM SUPPLEMENTATION

The following statement should be included in package inserts of medicines containing potassium for the purpose of potassium supplementation (under “pharmacological action”):

“This medicine contains potassium (salt to be named). It has not been proven that this dosage will necessarily prevent a significant potassium loss or correct an existing deficiency of potassium.”

2.37 REYE'S SYNDROME WARNING FOR MEDICINES CONTAINING ASPIRIN

The following warning should be included in all package inserts for aspirin containing products:

"Warning: Aspirin has been implicated in Reye's syndrome, a rare but serious illness in children and teenagers with chickenpox and influenza. A doctor should be consulted before aspirin is used in such patients."

2.38 LONG-ACTING SULPHONAMIDES

Refer to co-trimoxazole.

2.39 TAMOXIFEN

The following safety information (warning) should be included in the package inserts of all tamoxifen-containing products:

"An increased incidence of endometrial changes, including hyperplasia, polyps and cancer, have been reported in association with tamoxifen treatment. Any patients receiving, or who have previously received, tamoxifen and who report vaginal bleeding, should be promptly investigated."

Side effects and special precautions:

"Tamoxifen was shown to be genotoxic in some *in vivo* genotoxicity tests in rodents. Gonadal tumours in mice, and liver tumours in rats receiving tamoxifen, were reported in long-term studies. The clinical relevance of these findings has not been established."

2.40 TARTRAZINE (FD & C Yellow no 5)

The following warning should be included (under the heading of "WARNING") in the package insert of medicines which contain tartrazine:

"This product contains FD & C Yellow No 5 (Tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals. Although the overall incidence of Tartrazine sensitivity in the general population is currently thought to be low, it is frequently seen in patients who also have aspirin sensitivity."

2.41 TOPICAL TRETINOINS - statement on pregnancy and lactation

"Oral tretinoin has been shown to be teratogenic in a variety of animal species. Limited animal data urge caution in the use of preparations containing tretinoin during the first trimester of pregnancy."

"Topical tretinoin should be used during pregnancy only if the potential benefits outweigh the potential risks. In the case of an eventual pregnancy, the patient should inform her doctor."

"It is not known whether tretinoin is excreted in animal or human milk. However, because many medicines are excreted in human milk, caution should be exercised when applying topical tretinoin to nursing women. In this event, the product should not be used on the chest."

2.42 TRICYCLIC ANTIDEPRESSANTS

Unless the applicant can provide convincing evidence to the contrary, package inserts for tricyclic antidepressants should contain the following, although the wording need not be identical:

2.42.1 Side-effects and special precautions

"Peripheral anticholinergic side effects, notably dry mouth, constipation, urinary retention and pupillary dilatation with blurred vision and changes in visual accommodation. When anticholinergic effects are severe, the medicine should be discontinued or reduced."

"Drowsiness or excessive sedation may be caused in certain patients. On the other hand, disorientation and agitation, insomnia and restlessness can also occur with normal doses. The risks of central nervous system depression are greater when administered together with other central nervous system depressants, e.g. alcohol, barbiturates."

"NOTE: Elderly patients are more prone to all these effects, and therapy should be initiated at lower than standard doses in the elderly."

Special Precautions:

"At the time of initiation of therapy, patients should be advised not to drive a motor vehicle, climb dangerous heights or operate dangerous machinery for at least several days. In these situations, impaired decision making could lead to accidents."

"Caution should be exercised with patients suffering from a depressive phase of manic depressive psychosis, as occasionally hypomania or mania can be precipitated in such patients. Withdraw the drug if the depression turns into a manic phase."

"In elderly male patients suffering from prostatism, urinary retention may be precipitated."

"In patients suffering from cardiac disease, special caution should be observed because of the occasional problems of tachycardia, dysrhythmias orthostatic hypotension and other unwanted effects on blood pressure, aggravation of conduction disturbances and electrocardiographic abnormalities. Regular cardiological and electrocardiographic examination is advised."

"Epilepsy may be aggravated."

"The medicine should not usually be given to patients receiving other central nervous system depressants, for e.g. barbiturates, and to patients receiving monoamine oxidase inhibitors - only after a suitable interval has elapsed (the drugs may be given together if the dosages are carefully controlled, preferably in hospital). The pressor effects of the direct-acting sympathomimetic agents, adrenaline and noradrenaline, are enhanced, and the use of local anaesthetics containing these vasoconstrictors should be avoided as hypertensive reactions may occur. The simultaneous administration of anticholinergic agents may be dangerous. The hypotensive effect of certain antihypertensive agents may be reduced."

"Narrow-angle glaucoma may be aggravated."

"Withdraw the drug if allergic skin reactions appear."

2.42.2 Contra-Indications

"The acute-phase of myocardial infarction. Administration is not advised during the first trimester of pregnancy, unless there are compelling reasons for its use."

2.42.3 Overdosage

"Overdosage and poisoning may be characterised by central nervous system depression or excitation, severe anticholinergic effects and cardiotoxicity. The following symptoms and signs are characteristic of acute overdosage: drowsiness, restlessness, ataxia, stupor, coma, pyrexia, palpitations, tachycardia, cardiac arrhythmias, hypotension, and in severe cases, respiratory depression.

Epileptiform seizures may occur. Mixed poisoning with other central nervous system depressants is not uncommon."

2.42.4 Special warning

"This medicine should at all times be kept out of the reach of children, as even small doses may be fatal to them."

2.43 TRICYCLIC ANTIDEPRESSANTS: Acceptable claims

Serious depressive conditions such as major depressive illness, reactive depression and secondary depression. The following reflects what is defined under the various disorders:

Major depressive illness:

- Endogenous depression, unipolar depression, bipolar depression (manic-depressive psychosis), masked depression;
- Reactive depression:
- Neurotic depression;
- Secondary depression:
- Depression associated with alcoholism, schizophrenia, and Parkinsonism depression associated with personality disorder, depression caused by medicines and senility with depression.

The claims for enuresis and other states, such as phobic anxiety disturbances, obsessive compulsive disturbances and chronic pain, which may benefit from the administration of tricyclic antidepressants, may be considered but will require the submission of substantiating data.

2.44 SAFETY UPDATE OF SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs)

2.44.1 The package inserts for fluoxetine-containing products should include under CONTRAINDICATIONS "Safety and efficacy in children have not been established."

2.44.2 The Council resolution relating to the use of SSRIs in children under the age of 18 years old should be applicable to fluvoxamine-containing products. There is no data to show that this does not apply to fluvoxamine.

2.44.3 The package inserts for products which contain the following medicines fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, escitalopram, venlafaxine, mirtazepine and bupropion should include the following:

Warnings:

"Patients with major depressive disorder, both adults and children, may experience worsening of their depression and or the emergence of suicidal ideation and behaviour, whether or not they are taking antidepressant medicines. This risk may persist until significant remission occurs. A casual role, however, for antidepressant medicine in inducing such behaviour has not been established.

Patients being treated with [PROPRIETARY NAME] should, nevertheless, be observed closely for clinical worsening and suicidality, especially at the beginning of a course of therapy or at any time of dose changes, either increases or decreases.

Because of the possibility of co-morbidity between major depressive disorder and other psychiatric and non-psychiatric disorders, the same precautions observed when treating patients with major depressive disorders should be observed when treating patients with other psychiatric and non-psychiatric disorders.

The following symptoms have been reported in patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and non-psychiatric:

anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness, impulsivity, akathisia, hypomania, and mania. Although a casual link between the emergence of suicidal impulses has not been established, consideration should be given to changing the therapeutic regimen, including possibly discontinuing [PROPRIETARY NAME], in patients for whom such symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision is made to discontinue treatment, [PROPRIETARY NAME] should be tapered (See PRECAUTIONS and DOSAGE AND DIRECTIONS FOR USE."

2.45 NEW SAFETY INFORMATION ON THE USE OF SSRIs IN CHILDREN UNDER THE AGE OF 18 YEARS

2.45.1 The package inserts for products containing paroxetine, venlafaxine, citalopram, and sertraline should include:

(i) under CONTRAINDICATIONS : "Children under the age of 18 years. (See WARNINGS and SIDE EFFECTS AND SPECIAL PRECAUTIONS.)"

(ii) under WARNINGS : "Safety and efficacy in children under 18 years of age have not been established. (See CONTRAINDICATIONS and SIDE EFFECTS AND SPECIAL PRECAUTIONS.)"

(iii) under SIDE EFFECTS AND SPECIAL PRECAUTIONS, subheading 'Side Effects' : "In children reports of hostility, suicidal ideation and self-harm."

(iv) under SIDE EFFECTS AND SPECIAL PRECAUTIONS, subheading 'Special Precautions' : "Safety and efficacy in children under 18 years of age have not been established. In clinical trials in Major Depressive Disorder, there were increased reports of hostility and suicide-related adverse events such as suicidal ideation and self-harm. (See CONTRAINDICATIONS)."

(v) under DOSAGE AND DIRECTIONS FOR USE : information on the tapering of the dose on discontinuation of the product must be provided and cross-referenced to symptoms of withdrawal under SIDE EFFECTS AND SPECIAL PRECAUTIONS.

(vi) under SIDE EFFECTS AND SPECIAL PRECAUTIONS, that abrupt discontinuation of the product can lead to discontinuation effects, and list clearly the associated adverse events.

2.45.2 All package inserts of SSRIs including generic products should include the information as above in 12.42.1 (i) – (vi)

2.46 L-TRYPTOPHAN CONTAINING PRODUCTS: Statement on eosinophilia myalgia syndrome

The following statement should be included under "WARNINGS" in the package inserts of products containing L-Tryptophan:

"In the USA the Eosinophilia Myalgia Syndrome has been associated with the intake of L-Tryptophan."

2.47 USE OF MEDICINES DURING PREGNANCY AND LACTATION

In cases where the safety of a medicine, with regard to its use in pregnancy and lactation, has not been established, the following warning should be included in the package inserts for those medicines.

"The safety of this preparation in pregnancy and lactation has not been established."

2.48 VITAMIN A INDICATIONS

2.48.1 The indications for formulations containing 100 000 I.U. or 200 000 I.U. vitamin A are to be:

- To decrease the risk of measles related complications and death in pre-school children with malnutrition and/or vitamin deficiency.
- Vitamin A deficiency states, e.g. night blindness (nyctalopia) and xerophthalmia.

2.48.2 The indication for formulations containing 100 000 I.U. or 200 000 I.U. vitamin A is:

- To decrease the risk and severity of respiratory infections and diarrhoea in pre-school children with malnutrition and/or vitamin A deficiency.

3 OTHER

3.1 CONTACT LENS SOLUTIONS EXEMPTION

THIS EXEMPTION SPECIFICALLY DOES NOT APPLY TO ARTIFICIAL TEAR SOLUTIONS.

Contact lens solutions are exempted from package insert requirements, provided that:

a) the relevant immediate container labels and cartons (if any) contain the necessary information that would normally be required on the package insert;
b) such labels are fully bilingual;
c) no advertising matter of reference to other products be included on such labels; and
d) the draft labels be submitted to this office for prior approval.

3.2 DEPENDENCE PRODUCING POTENTIAL OF MEDICINES

Warnings concerning the dependence-producing potential of certain substances may be made known to the professionals.

3.3 DICYCLOMINE IN INFANTS

The indication "infantile colic" and dosage schedule for children younger than six months of age, should not be included. A warning against its use in "infantile colic" should be included.

Applicants to submit evidence of, as well as a motivation for, the dosage, dosage intervals, efficacy and safety of administration to children older than six months.

3.4 NON-CONTENT CLAIM: "CONTAINS NO ASPIRIN"

The use of the words "Contains no Aspirin" may not appear on the package insert or in the advertising of non-aspirin containing medicines. In terms of regulation 8(3), the wording may still appear on the immediate label of the medicine, provided that the type (or font) size is not bigger than the type size in which the APIs appear.

3.5 PACKAGE INSERTS/SLOGANS

Advertising (slogans), in package inserts, is not permissible.

3.6 WATER FOR INJECTION

General exemption from package insert requirements, in respect of sales packs of water for injection, will be considered provided that the following warning appears on at least the outer label in prominent type:

“Water for injection must not be administered on its own”

UPDATE HISTORY

Date	Reason for update	Version & publication
August 2009, January 2010	Removal of section 12 from the General Information guideline and inclusion in this guideline, with amendment of previous section 12.9 (Ace-inhibitors); Inclusion in this guideline of the following Communications to Industry, with amendment of Paracetamol information: *9.06 Package Insert Information Paracetamol Feb04 v1.doc – February 2004* *9.09 Vitamin A Indications Feb04 v1.doc – February 2004* *9.10 Warning on hyperglycaemia and diabetes mellitus with atypical antipsychotic agents Apr05 v1.doc – April 2005* *9.12 Safety update of Selective Serotonin Reuptake Inhibitors (SSRIs) Apr05 v1.doc - April 2005* *9.11 New safety information on the use of SSRIs in children under the age of 18 years Apr05 v1.doc – April 2005* *9.14 COX-2 Inhibitors & NSAIDs May06 v1.doc - May 2006* *9.20 ACE Inhibitors & ARBs Oct08 v1.doc - October 2008* Replacement of "Trade Name" with "Proprietary Name" where appearing	V1, Feb 2010
April 2014 Immediate effect 1 Nov 2014	New sections 2.4 All Antiretroviral Medicines and 2.32 Nucleoside/Nucleotide Reverse Transcriptase Inhibitors, and sections renumbered Implementation: New products Existing (registered) products	V2, May 2014
Immediate effect 01 March 2015	Version 3: Amendment to sections 2.22 and 2.31; deletion of Phenylbutazone and amendment of section 2.35 Implementation: New products Registered (existing) products	V3, Aug 2014
Immediate effect 01 March 2016	Version 4: Deletion of section 2.1, subsections 2.1.1, 2.1.2 and 2.1.3 Amendment to sections 2.2 on ACE inhibitors and ARBs under CONTRAINDICATIONS, WARNINGS AND SPECIAL PRECAUTIONS, INTERACTIONS, PREGNANCY AND LACTATION. Sections renumbered. Addition of section on standardised text for Bisphosphonate containing medicines (section 2.15). Implementation: New products Existing (registered) products	V4, July 2015