NIZORAL® TABLETS

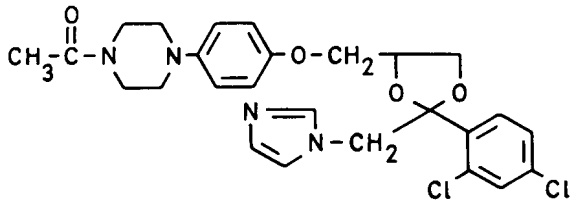
PRODUCT INFORMATION

NAME OF THE MEDICINE

Ketoconazole

The chemical name for ketoconazole is cis-1-acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy] phenyl] piperazine.

Ketoconazole has the following chemical structure:



CAS 65277-42-1 $C_{26}H_{28}Cl_2N_4O_4$ MW:531.44

DESCRIPTION

Ketoconazole is a synthetic antifungal for oral administration. It is a white or almost white powder, practically insoluble in water, freely soluble in methylene chloride, soluble in methanol and sparingly soluble in alcohol. The inactive ingredients are maize starch, lactose, povidone, microcrystalline cellulose, colloidal anhydrous silica and magnesium stearate.

PHARMACOLOGY

Ketoconazole exerts a fungistatic effect at plasma levels (mean approx. 3.5 micrograms/mL) achieved following an oral dose of 200 mg.

In vitro antifungal activity of ketoconazole against a number of organisms has been determined using an agar dilution procedure (Table 1). The clinical significance of these *in vitro* observations is not known. Despite the fact that some common fungi do not appear to be inhibited *in vitro* by a concentration of 4 micrograms/mL, ketoconazole has been shown to be clinically effective against them (see below).

Clinical efficacy of varying degrees has been demonstrated in patients with the following species of fungi (see **DOSAGE AND ADMINISTRATION**): *Trichophyton rubrum*, *T. mentagrophytes*, *Microsporum canis*, *Epidermophyton floccosum*, *Candida albicans*, *C. tropicalis*, *C. stellatoidea*, *Candida* spp., *Malassezia furfur*, *Paracoccidioides brasiliensis*, *Histoplasma capsulatum*, *Coccidioides immitis* and *Phialaphora* sppThe mode of action of ketoconazole appears to be similar to that of other imidazole antifungal agents. Ketoconazole has been shown to inhibit ergosterol biosynthesis in *C. albicans*, which leads to alterations in the composition and properties of the cell membrane. These alterations are probably the origin of increased susceptibility of the invasive yeast cell to lytic activity of the host-defence system.

Studies in rats have shown that at doses of 160 mg/kg, ketoconazole produces no enzyme induction.

Table 1 *: In vitro* anti fungal activity of ketoconazole*

Organism (No. tested)	Concentration, microgram/mL and cumulative % inhibited											Geometric Mean MIC
	Compound	<0.125	0.25	0.5	1	2	4	8	16	32	≥64	
Coccidioides immitis (10)	Keto-Conazole	20	90	100								0.23
Histoplasma capsulatum (9)	"	44	89	100								0.17
Blastomyces dermatitidis (12)	"	17	25	33	58	100						0.70
Candida** albicans(10)	"							20	40	60	100	27.85
C. Tropicalis (5)	"	20								40	100	13.82
Epidermophy-ton floccosum(9)	"	100										0.06
Microsporum canis(7)	"					17	50	67	100			6.35
Trichophyton mentagro-phytes(8)	"		12				25	100				5.19
Trichophyton rubrum(18)	"	6		17		22		56	78	100		7.70

* The usual dose of 200 mg/day provides mean plasma levels of approximately 3.5 micrograms/mL
** Ketoconazole has been shown to be clinically effective against both superficial and systemic infections of *Candida albicans*.

Pharmacokinetics

Following administration of a single 200 mg tablet, peak plasma levels of 0.5 to 4.5 micrograms/mL were reached within 1 to 2 hours after administration. The decline of the plasma levels is biphasic: a rapid elimination (alpha phase) with half life of approximately 2 hours during the first 10 hours and a slower elimination (beta phase) with half life of approximately 8 hours thereafter.

The fraction of the dose of ketoconazole absorbed from the gastrointestinal tract is extensively metabolised into a large number of metabolites. The major identified metabolic pathways are : oxidation and degradation of the imidazole and piperazine rings, oxidative O-dealkylation and aromatic hydroxylation.

About 13% of the dose is excreted in the urine, of which 2 to 4% is due to unchanged drug. The major route of excretion is with the faeces (approx. 57%) which contains, besides unchanged drug, mainly basic metabolites. The plasma protein binding is about 99%, mainly to the albumin fraction. In blood, 15% of the drug is distributed to the blood cell fraction, 84% is bound to the plasma proteins and 1% is present as unbound drug in the plasma water. Penetration into the CSF is poor. Ketoconazole, a weak dibasic agent, requires adequate gastric acidity for dissolution. Hypochlorhydria reduces the absorption of ketoconazole (see **DOSAGE AND ADMINISTRATION**). The recommended dose of 200 mg of ketoconazole produces serum concentrations of drug, which exceed the MIC values for most clinically important fungi.

INDICATIONS

Because of the risk for serious hepatic toxicity, NIZORAL tablets should be used only when the potential benefits are considered to outweigh the potential risks, taking into consideration the availability of other effective antifungal therapy.

Ketoconazole 200 mg tablets are indicated for the treatment of:

1. Systemic and deep mycoses (due to susceptible fungi) where other available antifungal therapies have failed or are contraindicated. Ketoconazole does not penetrate well in the CNS. Therefore, fungal meningitis should not be treated with oral ketoconazole.
2. Recalcitrant cases of superficial mycoses (due to susceptible fungi) which fail to respond to topical therapy and other conventional treatments.

CONTRAINDICATIONS

NIZORAL tablets are contraindicated in the following situations:

- In patients with a known hypersensitivity to ketoconazole or to any of the excipients

- In pregnant women

- In patients with acute or chronic liver disease

- Co-administration of the CYP3A4 substrates terfenadine, astemizole, bepridil, mizolastine, cisapride, disopyramide, dofetilide, halofantrine, levacetylmethadol (levomethadyl), quinidine, sertindole or pimozide with NIZORAL tablets is contraindicated since the increased plasma concentrations of these drugs arising from the interaction can lead to QT_c prolongation and rare occurrences of torsades de pointes

- Co-administration of domperidone is contraindicated since the combination can lead to QT_c prolongation

- Co-administration of Ergot Alkaloids (ergometrine, methylergometrin, ergotamine or dihydroergotamine) with NIZORAL tablets is contraindicated because of the increased risk for ergotism and other serious vasospastic disorders

- Co-administration of triazolam and oral midazolam

- Co-administration of nisoldipine

- Co-administration of eplerenone

- Co-administration of CYP3A4 metabolised HMG-CoA reductase inhibitors such as simvastatin and lovastatin (see **PRECAUTIONS-Interactions with other drugs**)
- Co-administration of irinotecan
- Co-administration of everolimus

PRECAUTIONS

WARNING: because of the risk for serious hepatotoxicity, NIZORAL tablets should be used only when the potential benefits are considered to outweigh the potential risks, taking into consideration the availability of other effective antifungal therapy.

Assess liver function, prior to treatment to rule out acute or chronic liver disease, and monitor at frequent and regular intervals during treatment, and at the first signs or symptoms of possible hepatotoxicity.

Oral ketoconazole has a potential for clinically important drug interactions (see **PRECAUTIONS - Interactions with other drugs**).

Hepatotoxicity

Very rare cases of serious hepatotoxicity, including cases with a fatal outcome or requiring liver transplantation have occurred with the use of oral ketoconazole. Some patients had no obvious risk factors for liver disease. Cases have been reported that occurred within the first month of treatment, including some within the first week.

The cumulative dose of the treatment is a risk factor for serious hepatotoxicity. Factors which may increase the risk of hepatitis are: prolonged treatment with NIZORAL tablets, females over 50 years of age, previous treatment with griseofulvin, a history of liver disease, known drug intolerance and concurrent use of medication which compromises liver function. A period of one month should be allowed between cessation of griseofulvin treatment and commencement treatment with NIZORAL tablets because of an apparent association between recent griseofulvin therapy and hepatic reactions to NIZORAL tablets.

Monitor liver function in all patients receiving treatment with NIZORAL tablets (see **Monitoring of hepatic function)**

Patients should be instructed to promptly report to their physician signs and symptoms suggestive of hepatitis such as anorexia, nausea, vomiting, fatigue, jaundice, abdominal pain or dark urine. In these patients, treatment should be stopped immediately and liver function should be conducted.

Monitoring of hepatic function

Monitor liver function in all patients receiving treatment with NIZORAL tablets. Monitor liver function prior to treatment to rule out acute or chronic liver disease (see **CONTRAINDICATIONS**), after two weeks of treatment and then on a monthly basis and at the first signs or symptoms of possible hepatic toxicity. When the liver function tests indicate liver injury, the treatment should be stopped immediately.

A risk and benefit evaluation should be made before oral ketoconazole is used in cases of non-life threatening diseases requiring long treatment periods.

In patients with elevated liver enzymes, or who have experienced liver toxicity with other drugs, treatment should not be started unless the expected benefit exceeds the risk of hepatic injury. In such cases, close monitoring of the liver enzymes is necessary.

Monitoring of adrenal function

NIZORAL has been shown to reduce the cortisol response to ACTH stimulation in healthy volunteers given daily doses of 400 mg or more. Adrenal function should be monitored in patients with adrenal insufficiency or with borderline adrenal function, in patients under prolonged periods of stress (e.g. major surgery, intensive care), and in patients on prolonged therapy presenting signs and symptoms suggestive of adrenal insufficiency.

Use in pregnancy

Category B3

Ketoconazole has been shown to be teratogenic (syndactylia and oligodactylia) and embryotoxic in rats given 80mg/kg/day. There are no adequate and well-controlled studies in pregnant women. Ketoconazole should not be used during pregnancy unless, in the judgement of the treating clinician, such use is deemed essential for the patient's welfare and the expected benefits outweigh the potential risks.

Use in lactation

Ketoconazole is excreted into human milk. Therefore, mothers who are under treatment with NIZORAL tablets should not breast-feed.

Use in children

The safety of ketoconazole in children has not yet been established.

Interaction with other medicines

The absorption of ketoconazole is impaired when gastric acidity decreases. The concomitant use of oral ketoconazole with drugs that reduce gastric acidity or drugs that suppress gastric acid secretion should be avoided. (see **DOSAGE AND ADMINISTRATION**).

Ketoconazole is a potent inhibitor of the cytochrome P450 3A4 system. Concomitant administration of oral ketoconazole with other drugs metabolised by this enzyme system may affect the metabolism and result in a change in clinical effect of the drugs used, including side effects.

The clinical observed interactions together with potential reactions are discussed below.

Effects of ketoconazole on other drugs –

- Co administration of the CYP3A4 substrates terfenadine, astemizole, bepridil, mizolastine, cisapride, disopyramide, dofetilide, halofantrine, levacetylmethadol (levomethadol), quinidine, sertindole or pimozide with NIZORAL tablets is contraindicated since the increased plasma concentrations of these drugs arising from the interaction can lead to QT_c prolongation and rare occurrences of torsades de pointes.
- Co-administration of domperidone is contraindicated since the combination can lead to QT_c prolongation
- Co-administration of triazolam or oral midazolam is contraindicated because of an exaggerated and prolonged pharmacodynamic response
- Co-administration of ergot alkaloids such as dihydroergotamine, ergometrine (ergonovine), ergotamine and methylergotamine (methylergonovine)
- Co-administration of nisoldipine
- Co-administration of eplerenone
- Co-administration of irinotecan

- Co-administration of everolimus

When co-administered with oral ketoconazole the following drugs should be used with caution, and their plasma concentrations and effects or side effects should be monitored. Their dosage, if administered with ketoconazole, should be reduced if necessary. This should be considered when prescribing concomitant medication.

HIV protease inhibitors (such as indinavir and saquinavir): *In vitro* inhibition of the metabolism of these drugs has been demonstrated. However, clinically relevant interaction with the metabolism of ritonavir is not expected.

**Amprenavir: produced increased accumulation and decreased clearance of ketoconazole. This interaction should be monitored carefully for possible liver toxicity during co-administration of both drugs.*

Atazanavir: Coadministration of ketoconazole has only been studied with atazanavir without ritonavir (negligible increase in atazanavir AUC and C_{max}). Plasma levels of both atazanavir and ritonavir may be increased by ketoconazole and itraconazole. High doses of ketoconazole and itraconazole (>200mg/day) should be used cautiously with atazanavir and ritonavir.

Darunavir: Ketoconazole, itraconazole and voriconazole are potent inhibitors as well as substrates of CYP3A. Concomitant systemic use of ketoconazole, itraconazole or voriconazole and darunavir and ritonavir may increase plasma concentrations of darunavir. Simultaneously. plasma concentrations of ketoconazole, itraconazole or voriconazole may be increased by darunavir and ritonavir. This was confirmed in an interaction trial where the concomitant administration of ketoconazole (200 mg b.i.d.) with darunavir (400 mg b.i.d.) and ritonavir (100 mg b.i.d.) increased exposure of ketoconazole and darunavir by 212% and 42%, respectively. When coadministration is required, the dailv dose of ketoconazole or itraconazole should not exceed 200 mg.

Indinavir: Administration of indinavir 600 mg tds with ketoconazole 400 mg daily resulted in a 20% reduction in AUC_{0-8hr} and 31% reduction in C_{max} for indinavir compared to indinavir 800mg tds alone. A dosage reduction of indinavir to 600 mg every 8 hours should be considered when indinavir and ketoconazole are coadministered.

Nevirapine: Ketoconazole and nevirapine should not be given concomitantly.

Alcohol: Rare instances of a disulfiram-like reaction to alcohol have been reported. This was characterised by flushing, rash, peripheral oedema, nausea and headache. All symptoms resolved within a few hours.

Cyclosporine, tacrolimus, sirolimus, methylprednisolone, budesonide, dexamethasone, carbamazepine, busulphan, vinca alkaloids, docetaxel, trimetrexate, rifabutin, sildenafil, digoxin, ebastine, erlotinib, imatinib, quetiapine, **solifenacin:** Ketoconazole, when administered orally, may alter the metabolism of these drugs resulting in elevation of plasma concentration. Dosage adjustment may be required in these instances.

Coumarin-like drugs: Ketoconazole, when administered orally, may enhance the anticoagulant effect. Careful monitoring is required when administered with ketoconazole.

Fluticasone: Ketoconazole, when administered orally, may increase the systemic exposure to fluticasone propionate after a single inhalation, resulting in a greater reduction of plasma cortisol as compared with fluticasone propionate alone.

Theoretical interactions:

Buspirone, alfentanil, phenytoin, alprazolam, cilostazol, eletriptan, fentanyl, midazolam IV, repaglinide, tolterodine: Ketoconazole, when administered orally, may alter the metabolism of these drugs resulting in elevation of plasma concentration. Dosage adjustment may be required in these instances.

Oral hypoglycaemic agents: Since severe hypoglycaemic episodes have been reported when oral hypoglycaemic agents are administered with other oral imidazole agents, care should be exercised when giving ketoconazole.

CYP3A4-metabolised calcium channel blockers (such as dihydropyridines and verapamil), CYP3A4-metabolised HMG-Co A reductase inhibitors (such as simvastatin, atrovastatin and lovastatin): There is a potential for increased plasma concentrations of these drugs when administered concomitantly with ketoconazole.

Brotizolam: An interaction of brotizolam with another azole antifungal has been observed. Care should be exercised if given concomitantly with ketoconazole.

Reboxetine: The metabolic routes for reboxetine are insufficiently characterised to permit prediction of its potential interactions. Caution should be exercised if given concomitantly with ketoconazole.

Potential interactions that have been excluded:

Loratadine, fexofenadine: Oral ketoconazole has been shown to increase the plasma concentrations (AUC) of both loratadine and fexofenadine. However, no change in the QT interval was observed, nor was there any change in the incidence of adverse events.

Other drugs that affect ketoconazole –

Demonstrated interactions:

Rifampicin, rifabutin, isoniazid, nevirapine, phenytoin, carbamazepine: These enzyme-inducing drugs significantly reduce the bioavailability of ketoconazole. Rifampicin and isoniazid should not be used concomitantly with oral ketoconazole. The combination of ketoconazole with potent enzyme inducers is not recommended.

Ritonavir: Ritonavir increases the bioavailability of ketoconazole. A dose reduction of oral ketoconazole should be considered when these drugs are given concomitantly.

Theoretical interactions:

Rifabutin: The use of ketoconazole tablets with these drugs may lower the plasma concentration of ketoconazole.

ADVERSE EFFECTS

****Clinical Trial Data***

Clinical trial data between 1977 to 2002 identified 92 clinical trials of varying degrees of quality and design and purpose of NIZORAL Tablets. 4735 subjects including patients and healthy volunteers participated in these trials. The safety information obtained from these subjects was used to derive the following adverse event profile for NIZORAL tablets.
The safety of NIZORAL Tablets was evaluated in 4735 subjects in 92 clinical trials where NIZORAL Tablets were administered to treat a fungal infection or to healthy volunteers.

*Adverse drug reactions that were reported in ≥1% of NIZORAL Tablets-treated subjects are shown in **Table 2**.*

Table 2. Adverse Drug Reactions Reported in ≥1% of 4735 NIZORAL Tablets-treated Subjects in 92 Clinical Trials

System Organ Class	*Preferred Term*	*%*
Gastrointestinal Disorders	*Abdominal pain*	*1.2*
	Diarrhoea	*1.8*
	Nausea	*2.5*
Hepato-biliary Disorders	*Hepatic function abnormal*	*1.2*
Nervous System Disorders	*Headache*	*2.4*

Additional adverse drug reactions that occurred in <1% of NIZORAL Tablets-treated subjects in the clinical datasets are listed in ***Table 3****.*

Table 3. Adverse Drug Reactions Reported in < 1% of 4735 NIZORAL Tablets-treated Subjects in 92 Clinical Trials

System Organ Class
Preferred Term
Endocrine Disorders
Gynaecomastia
Eye Disorders
Photophobia
Gastrointestinal Disorders
Abdominal pain upper
Constipation
Dry mouth
Dysgeusia
Dyspepsia
Flatulence
Tongue discolouration
Vomiting
General Disorders and Administration Site Conditions
Asthenia
Chills
Fatigue
Hot flush
Malaise
Oedema peripheral
Pyrexia
Hepato-biliary Disorders
Hepatitis
Jaundice
Immune System Disorders
Anaphylactoid reaction
Investigations
Platelet count decreased
Metabolism and Nutrition Disorders
Alcohol intolerance
Anorexia

Hyperlipidaemia

Increased appetite

Musculoskeletal and Connective Tissue Disorders

Myalgia

Nervous System Disorders

Dizziness

Paraesthesia

Somnolence

Psychiatric Disorders

Insomnia

Nervousness

Reproductive System and Breast Disorders

Menstrual disorder

Respiratory, Thoracic and Mediastinal Disorders

Epistaxis

Skin and Subcutaneous Tissue Disorders

Alopecia

Dermatitis

Erythema

Erythema multiforme

Pruritus

Rash

Urticaria

Xeroderma

Vascular Disorders

Orthostatic hypotension

**** Post-marketing Experience***

*Adverse drug reactions first identified during postmarketing experience with NIZORAL Tablets are presented by frequency category based on spontaneous reporting rates in **Table 4**. The frequencies are provided according to the following convention:*

Very common	*≥1/10*
Common	*≥1/100 and < 1/10*
Uncommon	*≥1/1,000 and <1/100*
Rare	*≥1/10,000 and <1/1,000*
Very rare	*<1/10,000, including isolated reports*

Table 4. Adverse Drug Reactions Identified During Postmarketing Experience with NIZORAL Tablets by Frequency Category Estimated from Spontaneous Reporting Rates

Blood and the Lymphatic System Disorders	
Very rare	*thrombocytopenia*
Immune System Disorders	
Very rare	*allergic conditions including anaphylactic shock, anaphylactic reaction and angioneurotic oedema*
Endocrine Disorders	
Very rare	*adrenocortical insufficiency*

Nervous System Disorders	
Very rare	*reversible intracranial pressure increased (e.g. papilloedema, fontanelle bulging in infants)*
Hepato-biliary Disorders	
Very rare	*serious hepatotoxicity, including hepatitis cholestatic, biopsy-confirmed hepatic necrosis, cirrhosis, hepatic failure including cases resulting in transplantation or death. (see Section 4.4 Special warnings and special precautions for use)*
Skin and Subcutaneous Tissue Disorders	
Very rare	*photosensitivity*
Musculoskeletal, Connective Tissue and Bone Disorders	
Very rare	*arthralgia*
Reproductive System and Breast Disorders	
Very rare	*erectile dysfunction; with doses higher than the recommended therapeutic dose of 200 or 400mg daily azoospermia*

At 200 mg daily, a transient fall in the plasma testosterone levels may occur. These usually normalise within 24 hours. During long-term therapy at 200 mg daily, plasma testosterone levels do not usually differ from controls.

Note. In rats increased fragility of long bones, leading in some cases to fractures, was observed after 3 to 6 months of treatment with ketoconazole. A variety of other hormonally related disturbances were also noted in the rat. Similar adverse effects have so far not been reported in man.

DOSAGE AND ADMINISTRATION

Adults: The recommended dose of NIZORAL is a single daily administration of 200 mg (one tablet) with food.

Notes

1. The absorption of ketoconazole is impaired when gastric acidity is decreased. Patients who are receiving acid neutralising medicines (e.g. antacids) should take these drugs at least 2 hours after the intake of NIZORAL. In patients with achlorhydria, such as certain AIDS patients and patients on drugs that suppress gastric acid secretion (e.g. H_2-antagonists, proton pump inhibitors), it is advisable to take NIZORAL with an acidic drink (pH 2.5-3) such as a cola beverage.
2. Follow up studies have generally reported low relapse rates following cessation of therapy varying between 0 - 37.5%. A further study reported a 75% relapse rate but this study included patients whose disease had not completely cleared clinically or mycologically.
3. The optimum duration of therapy with ketoconazole is not clearly established. Superficial mycoses appear to respond within 2 - 4 weeks. Systemic mycoses (other than candidosis) require prolonged treatment (3-6 months).
4. Generally, treatment should be continued until all clinical and laboratory tests indicate that active fungal infection has subsided. Treatment should be stopped immediately and liver function testing should be conducted when signs and symptoms suggestive of hepatitis such as anorexia, nausea, vomiting, fatigue, jaundice, abdominal pain or dark urine occur (see **CONTRAINDICATIONS – MONITORING HEPATIC FUNCTION**).
5. Depending on the type of infection being treated (see note 3 above) the dose may be increased from 200 mg/day to 400 mg/day if clinical response is considered inadequate after a reasonable trial period. A higher incidence of adverse effects may be anticipated with the higher doses.

OVERDOSAGE

There is no known antidote to ketoconazole.

**Symptoms:*

Adverse drug reactions reported by patients taking high doses of NIZORAL are available in 6 clinical trials in a total of 459 patients where NIZORAL was administered at doses of 1,200 mg daily either in tablet form or as an oral suspension. The most commonly reported adverse drug reactions were nausea (27.2%), fatigue (including somnolence and lethargy) (14.2%), vomiting (12.6%), gastrointestinal pain (including abdominal discomfort, gastrointestinal disorder, stomach discomfort) (12.0%), anorexia (including weight decreased, decreased appetite) (7.4%), flushing (including hyperhidrosis) (6.3%), oedema (5.7%), gynaecomastia (4.8%), rash (including eczema, purpura, dermatitis) (3.3%), diarrhoea (2.2%), headache (2.0%), dysgeusia (1.3%), and alopecia (1.1%).

Treatment:

In the event of acute accidental overdosage, treatment consists of supportive and symptomatic measures. **Within the first hour after ingestion, activated charcoal may be administered. Activated charcoal may reduce absorption of the drug if given within one or two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected.*

. Poisons Information Centre telephone numbers are:

- Australia: **13 11 26**
- New Zealand: 0800 POSION or 0800 764 766

PRESENTATION

NIZORAL ketoconazole 200 mg tablets (white, scored, marked K/200, Janssen on reverse) supplied in foil strips or blisters in cartons of 30 tablets and 10 tablets.

Storage

Store below 25^{o}C. Store in a dry place.

SPONSOR

JANSSEN-CILAG Pty Ltd, 1-5 Khartoum Road Macquarie Park NSW 2113 Australia

POISON SCHEDULE OF THE MEDICINE

Schedule 4

Date of TGA approval: 23 May 2011

Date of most recent amendment:

* Please note changes (presented as **italicised text*) in Product Information.