# New Zealand Data Sheet

## 1. PRODUCT NAME

Nyefax® Retard modified-release tablet

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each modified-release tablet contains 20 mg nifedipine.

**Excipient(s) with known effect**

Contains lactose monohydrate. For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Modified-release tablets.
Pale pink, biconvex, film-coated tablet of 7 mm diameter.

## 4. CLINICAL PARTICULARS

### 4.1. Therapeutic indications

- Prophylaxis of chronic stable angina pectoris (angina of effort) in combination with a beta blocker or as monotherapy.
- Treatment of hypertension.

### 4.2. Dose and method of administration

**Dose**

**Recommended usual dose**
As far as possible the treatment must be tailored to the needs of the individual according to the severity of the disease and the patient's response.

Depending on the clinical picture in each case, the basic dose must be introduced gradually. In patients with impaired liver function careful monitoring and, in severe cases, a dose reduction may be necessary.

***Adults***

Unless otherwise prescribed, the following dosage guidelines apply for adults:

**In Chronic stable angina pectoris (angina of effort)**
1 Nyefax Retard tablet twice daily (2 x 20 mg/day).
If higher dosages are necessary, the dose can be increased in stages up to a maximum of 60 mg daily.

**In hypertension**
1 Nyefax Retard tablet twice daily (2 x 20 mg/day).
If higher dosages are necessary, the dose can be increased in stages up to a maximum of 60 mg daily.

Co-administration with CYP 3A4 inhibitors or CYP 3A4 inducers may result in the recommendation to adapt the nifedipine dose or not to use nifedipine at all (refer to section 4.5).

**Duration of Treatment**
Treatment may be continued indefinitely.

Because Nyefax Retard has a pronounced anti-ischaemic and anti-hypertensive action, it should be discontinued gradually, particularly when high doses are used.

***Special Population***

Use in elderly

Based on the available pharmacokinetic data for nifedipine modified release tablets no dose adjustment is required in elderly patients over 65 years old.

Hepatic impairment

In patients with mild, moderate or severe impaired liver function, careful monitoring and a dose reduction may be necessary. The pharmacokinetics of nifedipine has not been investigated in patients with severe hepatic impairment (refer to sections 4.3, 4.4 and 5.2).

Renal Impairment:

No dosing adjustments required for patients with renal impairment.

***Paediatric population***

The safety and efficacy of nifedipine modified release tablet in children below 18 years has not been established.

***Method of Administration***

Tablets should be swallowed whole with a glass of water with or without food. Tablets should not be crushed or chewed. Grapefruit and its juice should be avoided.

The recommended dosage interval for Nyefax Retard is about 12 hours and should not be less than 4 hours.

## 4.3. Contraindications

Nyefax Retard must not be used in cases of known hypersensitivity to nifedipine or other dihydropyridines.

Nyefax Retard should not be used in patients with cardiogenic shock, unstable angina, clinically significant aortic stenosis and during or within a month of a myocardial infarction.

Nyefax retard should not be used for the treatment of acute angina attacks.

Nyefax retard should not be used for secondary prevention of myocardial infarction.

Nyefax retard should not be administered to patients with a history of gastro-intestinal obstruction, oesophageal obstruction, or and degree of reduced intestinal lumen diameter of the intestinal tract. It must not be used in patients with a Kock pouch (ileostomy after proctocolectomy). It is also contra-indicated in patients with inflammatory bowel disease. Nifedipine must not be used in combination with rifampicin because efficient plasma levels of nifedipine may not be obtained due to enzyme induction.

## 4.4. Special warnings and precautions for use

Tablets should be swallowed whole; they should not be crushed or chewed.
Care must be exercised in patients with very low blood pressure (severe hypotension with systolic pressure less than 90 mmHg) in cases of manifest heart failure and in the cases of severe aortic stenosis.

Nyefax retard should not be used during pregnancy unless the clinical condition of the woman requires treatment with nifedipine. It should be reserved for women with severe hypertension who are unresponsive to standard therapy.

Care must be exercised in pregnant women (refer to section 4.6), when administering nifedipine in combination with i.v. magnesium sulfate, owing to the possibility of an excessive fall in blood pressure, which could harm both mother and foetus.

Nyefax retard is not recommended for use in breastfeeding as it has been reported to be excreted in human milk and the effects of nifedipine exposure to the infant are not known.

In patients with mild, moderate or severe impaired liver function, careful monitoring and a dose reduction may be necessary due to the duration of action of the Nyefax Retard formulation. The pharmacokinetics of nifedipine have not been investigated in patients with severe hepatic impairment (refer to section 4.2 and 5.2). Therefore, nifedipine should be used with caution in patients with severe hepatic impairment.

Nyefax retard can be used with beta-blockers and other antihypertensives but there's a possibility of additive anti-hypertensive effects which could lead to postural hypotension.

Caution should be taken in patients with poor cardiac reserve as there is a potential risk of deterioration of heart failure.

Nifedipine is metabolised via the cytochrome P450 3A4 system. Medicines that are known to either inhibit or to induce this enzyme system may therefore alter the first pass or the clearance of nifedipine (refer to section 4.5).

Medicines which are weak to moderate inhibitors of the cytochrome P450 3A4 system and therefore may lead to increased plasma concentrations of nifedipine, are, e, g.:

- macrolide antibiotics (e.g. erythromycin)
- anti-HIV protease inhibitors (e.g. ritonavir)
- azole antimycotics (e.g. ketoconazole)
- the antidepressants of nefazodone and fluoxetine
- valproic acid
- cimetidine

Upon co-administration with these medicines, the blood pressure should be monitored and if necessary, a reduction of the nifedipine dose should be considered.

Since this medicinal product contains lactose, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

For use in special populations (refer to section 4.2).

## 4.5. Interaction with other medicines and other forms of interaction

**Medicines that affect nifedipine**
Nifedipine is metabolised via the cytochrome P450 3A4 system, located both in the intestinal mucosa and in the liver. Drugs that are known to either inhibit or to induce this enzyme system may therefore alter the first pass (after oral administration) or the clearance of nifedipine (see Section 4.4).

The extent as well as the duration of interactions should be taken into account when administering nifedipine together with the following medicines:

*Rifampicin:* Rifampicin strongly induces the cytochrome P450 3A4 system. Upon co-administration with rifampicin, the bioavailability of nifedipine is distinctly reduced and thus its efficacy weakened. The use of nifedipine in combination with rifampicin is, therefore contraindicated (see Section 4.3).

Upon co-administration of known inhibitors of the cytochrome P450 3A4 system, the blood pressure should be monitored and, if necessary, a reduction in the nifedipine dose considered (see Sections 4.2 and 4.4). In the majority of these cases, no formal studies to assess the potential for a drug interaction between nifedipine and the drug(s) listed have been undertaken, thus far.

**Medicines increasing nifedipine exposure:**

- *macrolide antibiotics (e.g., erythromycin)*

- *anti-HIV protease inhibitors (e.g., ritonavir)*

- *azole anti-mycotics (e.g., ketoconazole)*

- *fluoxetine*

- *nefazodone*

- *cisapride*

- *valproic acid*

- *cimetidine*

- *diltiazem*

Upon co-administration of inducers of the cytochrome P450 3A4 system, the clinical response to nifedipine should be monitored and, if necessary, an increase in the nifedipine dose considered. If the dose of nifedipine is increased during co-administration of both medicines, a reduction of the nifedipine dose should be considered when the treatment is discontinued.

**Medicines decreasing nifedipine exposure:**

- *rifampicin (see above)*

- *phenytoin*

- *carbamazepine*

- *phenobarbital*

**Effects of nifedipine on other medicines**

Nifedipine may increase the blood pressure lowering effect of concomitant applied antihypertensives.

When nifedipine is administered simultaneously with ß -receptor blockers the patient should be carefully monitored, since deterioration of heart failure is also known to develop in isolated cases.

*Digoxin*: The simultaneous administration of nifedipine and digoxin may lead to reduced digoxin clearance and, hence, an increase in the plasma digoxin level. The patient should therefore be subjected to precautionary checks for symptoms of digoxin overdosage and, if necessary, the glycoside dose should be reduced.

*Quinidine:* Co-administration of nifedipine with quinidine may lower plasma quinidine levels, and after discontinuation of nifedipine, a distinct increase in plasma quinidine levels may be observed in individual cases. Consequently, when nifedipine is either additionally administered or discontinued, monitoring of the quinidine plasma concentration, and if necessary, adjustment of the quinidine dose are recommended. Blood pressure should be carefully monitored and, if necessary, the dose of nifedipine should be decreased.

*Tacrolimus*: Tacrolimus is metabolised via the cytochrome P450 3A4 system. Published data indicate that the dose of tacrolimus administered simultaneously with nifedipine may be reduced in individual cases. Upon co-administration of both drugs, the tacrolimus plasma concentrations should be monitored and, if necessary, a reduction in the tacrolimus dose considered.

**Medicine food interactions**
Grapefruit juice inhibits the cytochrome P450 3A4 system. Administration of nifedipine together with grapefruit juice thus results in elevated plasma concentrations and prolonged action of nifedipine due to a decreased first pass metabolism or reduced clearance. As a consequence, the blood pressure lowering effect of nifedipine may be increased. After regular intake of grapefruit juice, this effect may last for at least three days after the last ingestion of grapefruit juice. Ingestion of grapefruit/grapefruit juice is therefore to be avoided while taking nifedipine (see Section 4.2).

**Other forms of interaction**

Nifedipine may increase the spectrophotometric values of urinary vanillylmandelic acid, falsely. However, HPLC measurements are unaffected.

## 4.6. Fertility, pregnancy and lactation

### Pregnancy

Nifedipine should be avoided during pregnancy unless the clinical condition of the woman requires treatment with nifedipine (see section 4.4)

Animal studies have shown a variety of embryotoxic, placentotoxic and fetotoxic effects when administered during and after the period of organogenesis (refer to section 5.3).

From the clinical evidence available, a specific prenatal risk has not been identified. Although an increase in perinatal asphyxia, caesarean deliveries as well as prematurity and intrauterine growth retardation have been reported, it is unclear whether these reports are due to the underlying hypertension, its treatment or to a specific drug effect.

The available information is inadequate to rule out adverse drug effects on the unborn and newborn child. Therefore, any use in pregnancy requires a very careful individual risk benefit assessment and should only be considered if all other treatment options are either not indicated or have failed to be efficacious.

Acute pulmonary oedema has been observed when calcium channel blockers including nifedipine, have been used as a tocolytic agent during pregnancy, especially in cases of multiple pregnancies (twins or more), with the intravenous route and/or concomitant use of beta blockers.

**Breast-feeding**

Nyefax retard is not recommended for use in breastfeeding as it is excreted into breast milk and the effects of nifedipine exposure to the infant are not known. The concentration of nifedipine in breast milk is similar to the mother's serum concentration.

**Fertility**

***In vitro* fertilisation**

In single cases of *in vitro* fertilisation calcium-antagonists like nifedipine have been associated with reversible biochemical changes in the spermatozoa's head section that may result in impaired sperm function. In those men who are repeatedly unsuccessful in fathering a child by *in vitro* fertilisation, and where no other explanation can be found, calcium antagonists like nifedipine should be considered as possible causes.

## 4.7. Effects on ability to drive and use machines.

Reactions to the drug, which may vary in intensity from individual to individual, can impair the ability to drive or to operate machinery. This applies particularly at the start of the treatment, on changing the medication and in combination with alcohol.

## 4.8. Undesirable effects

Adverse drug reactions (ADRs) based on placebo-controlled studies with nifedipine sorted by CIOMS III categories of frequency (clinical trial data base: nifedipine n = 2661; placebo n = 1486; status: 22 Feb 2006 and the ACTION study: nifedipine n = 3825; placebo n = 3840) are listed below:

ADRs listed under "common" were observed with a frequency below 3% with the exception of oedema (9.9%) and headache (3.9%).

The frequencies of ADRs reported with nifedipine containing products are summarised in Table 1

below. With each frequency grouping, ADRs are presented in order of decreasing seriousness.

The frequencies are defined as:

Common ≥ 1/100 to < 1/10 (≥1% to <10%)
Uncommon ≥ 1/1000 to < 1/100 (≥0.1% to <1%)
Rare ≥ 1/10000 to < 1/1000 (≥0.01% to <0.1%)

*Table 1 Adverse drug reactions reported on clinical trial data*

| System Organ Class | Common<br>≥1% to <10% | Uncommon<br>≥0.1% to <1% | Rare<br>≥0.01% to <0.1% |
|---|---|---|---|
| Immune system disorders | | Allergic reaction<br>Allergic oedema/angioedema (incl. larynx oedema*) | Pruritus<br>Urticaria<br>Rash |
| Psychiatric disorders | | Anxiety reactions<br>Sleep disorders | |
| Nervous system disorders | Headache | Vertigo<br>Migraine<br>Dizziness<br>Tremor | Par-/Dysaesthesia |
| Eye disorders | | Visual disturbances | |
| Cardiac disorders | | Tachycardia<br>Palpitations | |
| Vascular disorders | Oedema (including peripheral oedema)<br>Vasodilatation | Hypotension<br>Syncope | |
| Respiratory, thoracic, and mediastinal disorders | | Nasal congestion<br>Nosebleed | |
| Gastrointestinal disorders | Constipation | Gastrointestinal<br>Abdominal pain<br>Nausea<br>Dyspepsia<br>Flatulence<br>Dry mouth | Gingival hyperplasia |
| Hepatobiliary disorders | | Transient increase in liver enzymes | |
| Skin and subcutaneous tissue disorders | | Erythema | |
| Musculoskeletal and connective tissue disorders | | Muscle cramps<br>Joint swelling | |
| Renal and urinary disorders | | Polyuria<br>Dysuria | |
| Reproductive system and breast disorders | | Erectile dysfunction | |

| System Organ Class | Common<br>≥1% to <10% | Uncommon<br>≥0.1% to <1% | Rare<br>≥0.01% to <0.1% |
|---|---|---|---|
| General disorders and administration site conditions | Feeling unwell | Unspecific pain<br>Chills | |

*= may result in life-threatening outcome

In dialysis patients with malignant hypertension and hypovolaemia a distinct fall in blood pressure can occur as a result of vasodilation.

**Post marketing adverse effects**

The ADRs identified during the ongoing market surveillance and for which a frequency could not be estimated are: agranulocytosis, leucopoenia, anaphylactic/anaphylactoid reaction, hyperglycaemia, hypoesthesia, somnolence, eye pain, chest pain (angina pectoris), dyspnoea, pulmonary oedema, vomiting, gastroesophageal sphincter insufficiency, intestinal ulcer, intestinal obstruction, bezoar, dysphagia, jaundice, toxic epidermal necrolysis, photosensitivity allergic reaction, palpable purpura, arthralgia and myalgia.

***Reporting of suspected adverse reactions***

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions
https://pophealth.my.site.com/carmreportnz/s/

## 4.9. Overdose

**Symptoms**

The following symptoms are observed in cases of severe nifedipine intoxication:

Disturbances of consciousness to the point of coma, a drop in blood pressure, tachycardia, bradycardia, hyperglycaemia, metabolic acidosis, hypoxia, cardiogenic shock with pulmonary oedema.

**Treatment**

As far as treatment is concerned, elimination of the active substance and restoration of stable cardiovascular conditions have priority. Elimination must be as complete as possible, including the small intestine, to prevent otherwise inevitable subsequent absorption of the active substance.

The benefit of gastric decontamination is uncertain.
1. Consider activated charcoal (50g for adults, 1g/kg for children) if patient presents within 1 hour of ingestion of toxic amount.

Late administration of activated charcoal has not been shown to be beneficial for sustained release preparations.
2. Consider further doses of activated charcoal every 4 hours if a clinically significant amount of sustained release preparation has been ingested with a single dose of an osmotic laxative.
3. Asymptomatic patients should be observed for at least 4 hours after ingestion or 12 hours If a sustained release preparation was used.

Haemodialysis serves no purpose, as nifedipine is not dialysable, but plasmapheresis is advisable (high plasma binding, relatively low volume of distribution).

Bradycardiac heart rhythm disturbances may be treated symptomatically with β-sympathomimetics, and in life-threatening bradycardiac disturbances of heart rhythm temporary pacemaker therapy can be advisable.

Hypotension as a result of cardiogenic shock and arterial vasodilation can be treated with calcium (10-20 mL of a 10% calcium gluconate solution administered slowly i.v. and repeated if necessary). As a result, the serum calcium can reach the upper normal range to slightly elevated levels. If an insufficient increase in blood pressure is achieved with calcium, vasoconstricting sympathomimetics such as dopamine or noradrenaline are additionally administered. The dosage of these drugs is determined solely by the effect obtained.

Additional liquid or volume must be administered with caution because of the danger of overloading the heart.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1. Pharmacodynamic properties

Pharmacotherapeutic group: selective calcium channel blockers with mainly vascular effect, ATC code: C08CA05

Nifedipine is a calcium antagonist of the 1,4-dihydropyridine type. Calcium antagonists reduce the transmembranal influx of calcium ions through the slow calcium channel into the cell. Nifedipine acts particularly on the cells of the myocardium and the smooth muscle cells of the coronary arteries and the peripheral resistance vessels. The main action of nifedipine is to relax the arterial smooth muscle in both the coronary and peripheral circulation. The formulation of Nyefax retard achieves slow release which allows for once-daily dosing.

In hypertension, the main action is peripheral vasodilation, hence reducing peripheral resistance. It is administered once-daily and provides 24-hour control of raised blood pressure. It

reduces blood pressure such that the percentage of lowering is proportional to the initial level. In normotensive individuals, nifedipine has little or no effect on blood pressure.

In angina, Nyefax Retard reduces peripheral and coronary resistance, leading to an increase in coronary blood flow, cardiac output, and stroke volume whilst decreasing afterload. It also submaximally dilates both clear and atherosclerotic coronary arteries, thus protecting the heart against coronary artery spasm and improving perfusion to the ischaemic myocardium . Additionally, it reduces the frequency of painful attacks and the ischaemic ECG changes irrespective of the relative contribution from coronary artery spasm or atherosclerosis.

Paediatric population:
Limited information on the difference between nifedipine and other antihypertensives is available. Antihypertensive effects have been demonstrated but dose recommendations, long-term safety and effect on cardiovascular outcome remained unestablished.

## 5.2. Pharmacokinetic properties

### Absorption

After oral administration nifedipine is rapidly and almost completely absorbed. The systemic availability of orally administered nifedipine is 45 – 56% owing to a first pass effect. Maximum plasma and serum concentrations are reached at 1.5 to 4.2 hours with nifedipine. Simultaneous food intake leads to delayed, but not reduced absorption.

*Table 2 Peak plasma concentrations* and *the time to reach peak plasma concentrations*

| Dose | $C_{max}$ (mg/l) | $T_{max}$ (h) |
|---|---|---|
| 20 mg | 26-74 | 1.6-4.2 |

### Distribution

Nifedipine is about 95% bound to plasma protein (albumin). The distribution half-life after intravenous administration was determined to be 5 to 6 minutes.

### Biotransformation

After oral administration, nifedipine is metabolised in the gut wall and in the liver, primarily by oxidative processes. These metabolites show no pharmacodynamic activity.

Nifedipine is excreted in the form of its metabolites predominantly via the kidney and about 5 – 15% via the bile in the faeces. The unchanged substance is recovered only in traces (below 0.1%) in the urine.

### Elimination

The terminal elimination half-life is 6 – 11 hours because of delayed absorption. No accumulation of the substance after the usual dose was reported during long-term treatment.

In cases of impaired kidney function no substantial changes have been detected in comparison with healthy volunteers.

In a study comparing the pharmacokinetics of nifedipine in patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment with those in patients with normal liver function, oral clearance of nifedipine was reduced by on average 48% (Child Pugh A) and 72% (Child Pugh B). As a result, AUC and Cmax of nifedipine increased on average by 93% and 64% (Child Pugh A) and by 253% and 171% (Child Pugh B), respectively, compared to patients with normal hepatic function. The pharmacokinetics of nifedipine have not been investigated in patients with severe hepatic impairment (refer to section 4.4).

In patients with hepatic impairment, the elimination half-life is distinctly prolonged, and the total clearance is reduced. Due to the duration of action of the formulation, Nyefax Retard monitoring is required for these patients and dose adjustments may be required.

## 5.3. Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of single and repeated dose toxicity, genotoxicity and carcinogenic potential.

### Acute toxicity

Acute toxicity has been investigated in various animal species and the individual results are listed in table 3.

*Table 3 Acute toxicity in various animal species*

| | **$LD_{50}$ (mg/kg)** | |
|---|---|---|
| | **oral** | **i.v.** |
| Mouse | 494 (421-572) * | 4.2 (3.8-4.6)* |
| Rat | 1022 (950-1087) * | 15.5 (13.7-17.5) * |
| Rabbit | 250-500 | 2-3 |
| Cat | ~ 100 | 0.5-8 |
| Dog | >250 | 2-3 |

- 95% Confidence interval

### Sub-acute and Sub-chronic Toxicity

Daily oral administration of rats (50 mg/kg body weight) and to dogs (100 mg/kg body weight) over periods of 13 and 4 weeks respectively were tolerated without toxic effects.

After parenteral (i.v.) administration dogs tolerated up to 0.1 mg/kg body weight/day for 6 days without damage. Daily i.v. administration of 2.5 mg/kg body weight in rats over a period of 3 weeks was also tolerated without signs of damage.

**Chronic Toxicity**

Dogs tolerated up to 100 mg/kg body weight as a daily oral dose over a period of 1 year without toxic damage. In rats, toxic effects occurred at concentrations above 100 ppm in the feed (about 5-7 mg/kg body weight).

**Carcinogenicity**

A long-term study in rats (2 years) yielded no evidence of a carcinogenic effect of nifedipine.

**Reproduction Toxicology**

Nifedipine has been shown to produce teratogenic findings in rats, mice and rabbits, including digital anomalies, malformation of extremities, cleft palates, cleft sternum and malformation of the ribs.

Digital anomalies and malformation of the extremities are possibly a result of compromised uterine blood flow but have also been observed in animals treated with nifedipine solely after the end of the organogenesis period.

Nifedipine administration was associated with a variety of embryotoxic, placentotoxic and foetotoxic effects, including stunted foetuses (rats, mice, rabbits), small placentas and underdeveloped chorionic villi (monkeys), embryonic and foetal deaths (rats, mice, rabbits) and prolonged pregnancy/decreased neonatal survival (rats; not evaluated in other species). All of the doses associated with the teratogenic, embryotoxic or foetotoxic effects in animals were maternally toxic and several times the recommended maximum dose for humans (refer to section 4.6).

**Mutagenicity**

To assess the mutagenic effects the Ames test, the Dominant-lethal test, and the Micronucleus test were performed in the mouse. No evidence of a mutagenic effect of nifedipine could be found.

# 6. PHARMACEUTICAL PARTICULARS

## 6.1. List of excipients

**Nyefax® Retard modified-release tablet** contains iron oxide black, iron oxide red, lactose monohydrate, macrogol 4000, magnesium stearate, methylcellulose, microcrystalline cellulose, polysorbate 80, pregelatinised maize starch, purified water, titanium dioxide.

## 6.2. Incompatibilities

Not applicable.

### 6.3. Shelf life

36 months.

### 6.4. Special precautions for storage

Blister pack: Store at or below 30°C.
Bottle plastic: Store at or below 25°C.

Protect from light and moisture.

### 6.5. Nature and contents of container

Blister pack, 30 tablets
Bottle plastic, 100 tablets
Not all pack sizes may be marketed.

### 6.6. Special precautions for disposal and other handling

Any unused medicine or waste material should be disposed of in accordance with local requirements.

## 7. MEDICINE SCHEDULE

Prescription medicine

## 8. SPONSOR

Douglas Pharmaceuticals Ltd
P O Box 45 027
Auckland 0651
New Zealand
Phone: (09) 835 0660

## 9. DATE OF FIRST APPROVAL

20 February 1986

## 10. DATE OF REVISION OF THE TEXT

18 September 2024

Summary table of changes

| Section Changed | Summary of new information |
|---|---|
| 4.1 | Removed treatment of coronary heart disease as a therapeutic indication |
| 4.2 | Removed Coronary Heart Disease<br>Removed '"Attending doctor will determine duration of use"<br>Added to method of administration: Do not crush or chew and avoid grapefruit juice. |
| 4.3 | Contraindications removed for breastfeeding and pregnancy<br>Added some more cardiovascular and gastrointestinal contraindications. |
| 4.4 | Added 'Do not crush or chew' as a precaution.<br>Removed outdated breastfeeding information.<br>Additional information concerning warnings for use during pregnancy included<br>Added the risk of hypotension with concomitant use of beta blockers. |
| 4.5 | Added a list of medicines that increase exposure and a list of medicines that reduce exposure.<br>Removed some medicines in the list of "interactions shown not to exist" section- removed the ones that are not available in NZ. |
| 4.6 | Pregnancy and breast-feeding sections revised<br>Minor editorial changes |
| 4.8 | Added some more post-marketing adverse effects.<br>Updated reporting URL |
| 4.9 | Removed gastric lavage with revised treatment plan for overdose. |
| 5.1 | Added more information on Mode of Action. |