NEW ZEALAND DATA SHEET

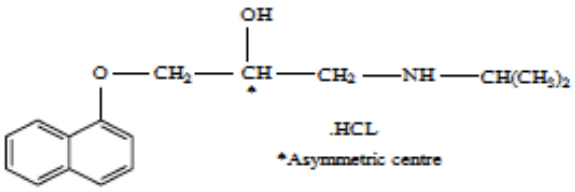
1. PRODUCT NAME

Drofate, 10 mg and 40 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg or 40 mg of propranolol hydrochloride.

Chemical Structure:



Chemical Name: 2-propanol, 1-[(1-methyl-ethyl)amino]-3-(1-naphthalenyloxy), hydrochloride, (±).

Molecular Formula: $C_{16}H_{21}NO_2$,HCl Molecular Weight: 295.8

CAS Registry Number: 318-98-9.

Excipient with known effect: lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Drofate 10mg tablets: Orange coloured, round, biconvex tablets, embossed with "P" and "10" on either side of the breakline on one side and plain on the other side.

Drofate 40 mg tablets: Green coloured, round, biconvex tablets, embossed with "P" and "40" on either side of the breakline on one side and plain on the other side.

The score line is not intended for breaking the tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Management of angina pectoris.
- Long term prophylaxis after recovery from acute myocardial infarction.
- Control of most forms of cardiac dysrhythmias.
- Control of essential and renal hypotension
- Prophylaxis of migraine.
- Control of anxiety and anxiety tachycardia
- Management of essential tremor.
- Adjunctive management of thyrotoxicosis and thyrotoxic crisis.
- Management of hypertrophic obstructive cardiomyopathy.
- Management of phaeochromocytoma (with an alpha-adrenoreceptor blocking medicine).

4.2 Dose and method of administration

Dose

Adults

Hypertension

A starting dose of 80 mg twice a day may be increased at weekly intervals according to response. The usual dose range is 160-320 mg per day. With concurrent diuretic or other anti-hypertensive drugs a further reduction of blood pressure is obtained.

Angina, Anxiety, Migraine and Essential Tremor

A starting dose of 40 mg two or three times daily may be increased by the same amount at weekly intervals according to patient response. An adequate response in anxiety, migraine and essential tremor is usually seen in the range 80-160 mg/day and in angina in the range 120-240 mg/day.

Dysrhythmias, Anxiety Tachycardia, Hypertrophic Obstructive Cardiomyopathy and Thyrotoxicosis

A dosage range of 10-40mg three to four times a day usually achieves the required response.

Post Myocardial Infarction

Treatment should start 5-21 days after myocardial infarction, with an initial dose of 40mg four times a day for 2-3 days. In order to improve compliance the total daily dose can thereafter be given as 80mg twice a day.

Phaeochromocytoma

To be used only with an alpha-adrenoreceptor blocking medicine.

Pre-operative

60mg daily for 3 days is recommended.

Non-operative malignant cases

30mg daily.

Maximum Tolerated Daily Dose

Do not halve the tablet.

Special populations

Paediatric population

The dose of Drofate should always be individually determined. The following doses are intended only as a guide.

Dysrhythmias, Phaeochromocytoma and Thyrotoxicosis

0.25-0.5mg/kg three or four times daily as required.

Migraine

Under age of 12: 20mg two or three times daily.

Over age of 12: The adult dose.

Elderly

Evidence concerning the relationship between the blood levels and age is conflicting. With regard to the elderly, the optimum dose should be individually determined according to clinical response.

Method of administration

The tablets are to be administered orally.

4.3 Contraindications

- Propranolol must not be used if there is a history of bronchospasm or bronchial asthma.

- Propranolol as with other beta-adrenoreceptor blocking medicines must not be used in patients with and of the following:
  - known hypersensitivity to the substance
  - second or third degree heart block
  - cardiogenic shock
  - uncontrolled heart failure
  - hypotension
  - severe peripheral arterial circulatory disturbances
  - untreated phaeochromocytoma
  - Prinzmetal's angina
  - bradycardia
  - sick sinus syndrome
  - metabolic acidosis
  - after prolonged fasting

4.4 Special warnings and precautions for use

Special care should be taken with patients whose cardiac reserve is poor. Beta- adrenoreceptor blocking medicines should be avoided in uncontrolled heart failure (see section 4.3 **Contraindications**). However, they may be used in patients whose signs of failure have been controlled.

Propranolol is contraindicated in severe peripheral arterial circulatory disturbances and may also aggravate less severe peripheral arterial circulatory disturbances.

Due to its negative effect on conduction time, caution must be exercised if propranolol is given to patients with first degree heart block.

Propranolol modifies the tachycardia of hypoglycaemia. Caution should be exercised in the concurrent use of propranolol and hypoglycaemic therapy in diabetic patients. Propranolol may prolong the hypoglycaemic response to insulin. Propranolol may mask signs of hypoglycaemia in diabetic patients on hypoglycaemic therapy.

Propranolol may mask the signs of thyrotoxicosis.

One of the pharmacological actions of beta-adrenoreceptor blocking medicines is to reduce heart rate. In the rare instance when symptoms may be attributable to the slow heart rate, the dose may be reduced.

In patients suffering from ischaemic heart disease, as with other beta-adrenoreceptor blocking medicines, treatment should not be discontinued abruptly. Either the equivalent dosage of another beta-adrenoreceptor blocking medicine may be substituted or the withdrawal of propranolol should be gradual.

Propranolol may cause a more severe reaction to a variety of allergens, when given to patients with a history of anaphylactic reaction to such allergens. Such patients may be unresponsive to the usual doses of adrenalin used to treat the allergic reactions.

Since the half-life may be increased in patients with significant hepatic or renal impairment, caution must be exercised when starting treatment and selecting the initial dose.

Propranolol must be used with caution in patients with decompensated cirrhosis.

In patients with portal hypertension, liver function may deteriorate and hepatic encephalopathy may develop. Propranolol may increase the risk of hepatic encephalopathy.

In patients with chronically obstructive lung diseases, the use of propranolol is not recommended.

Anaesthesia
Caution must be exercised when using anaesthetic agents with propranolol. It may be decided to discontinue therapy with beta-adrenoreceptor blocking medicines before surgery, in which case a gradual withdrawal is recommended. If it is decided not to discontinue therapy with beta-adrenoreceptor blocking medicines before surgery, care should be taken when using anaesthetic agents with propranolol. The anaesthetist should be informed and the choice of anaesthetic should be the agent with as little negative inotropic activity as possible. Use of beta-adrenoreceptor blocking medicines with anaesthetic medicines may result in attenuation of the reflex tachycardia and increase the risk of hypotension. Anaesthetic agents causing myocardial depression are best avoided.

4.5 Interaction with other medicines and other forms of interaction

Anaesthetics
Care should be taken when using anaesthetic agents with propranolol. The choice of anaesthetic should be the agent with as little negative inotropic activity as possible.

Class I antiarrhythmics
Care should be taken in prescribing a beta-adrenoceptor blocking medicine with a Class 1 antidysrhythmic agent such as disopyramide and quinidine as this may have potentiating effects on atrioventricular conduction time and induce negative inotroptic effect.

Adrenaline
Care should be taken in the parenteral administration of preparations containing adrenaline to patients taking beta-adrenoceptor blocking medicines as, in rare cases, vasoconstriction, hypertension and bradycardia may result.

Calcium channel blockers
Combined use of beta-adrenoceptor blocking drugs and calcium channel blockers with negative inotropic effects (eg. verapamil, diltiazem) can lead to prolongation of AV conduction.

Beta-adrenoceptor blocking medicines should be used with caution in combination with verapamil in patients with impaired ventricular function. The combination should not be given to patients with conduction abnormalities. Neither medicine should be administered intravenously with 48 hours of discontinuing the other.

Digitalis
Digitalis glycosides, in association with beta-blockers, may increase atrioventricular conduction time.

Cimetidine & Hydralazine
Concomitant use of cimetidine or hydralazine will increase, whereas concomitant use of alcohol will decrease, the plasma levels of propanolol.

Ergot derivatives
Care should be taken when using propranolol with ergotamine, dihydroergotamine or related compounds since vasopastic reactions have been reported in a few patients.

Indomethacin
The hypotensive effects of beta-blockers may be decreased when used concomitantly with prostaglandin synthetase inhibiting drugs, e.g. ibuprofen and indomethacin.

Chlorpromazine
Concomitant administration of propranolol and chloropromazine may result in an increase in plasma levels of both drugs. This may lead to an enhanced antipsychotic effect for chlorpromazine and an increased antihypertensive effect for propranolol.

Pharmacokinetic studies have shown that the following agents may interact with propranolol due to effects on the enzyme systems in the liver which metabolise propranolol and these agents: quinidine, propafenone, rifampicin, theophylline, warfarin, thioridazine and dihydropyridine calcium channel blockers e.g. nifedipine, nisoldipine, nicardipine, isradipine and lacidipine. Owing to the fact that blood concentrations of either agent may be affected, dosage adjustments may be needed to be made according to clinical judgement. ,

See also Warnings and Precautions for information on calcium antagonists, diabetes, antiarrhythmic drugs, lignocaine, anaesthesia and the perioperative period, catecholamine depleting agents and clonidine.

4.6 Fertility, pregnancy and lactation

Use in pregnancy (Category C)

As with all other medicines, propranolol should not be given in pregnancy unless its use is essential. There is no evidence of teratogenicity with propranolol. However, beta-adrenoreceptor blocking medicines reduce placental perfusion, which may result in intra-uterine foetal death, immature and premature deliveries. In addition, adverse effects (especially hypoglycaemia and bradycardia in the neonate and bradycardia in the foetus) may occur. There is an increased risk of cardiac and pulmonary complications in the neonate in the post-natal period.

Breast-feeding

Most beta-adrenoreceptors blocking medicines, particularly lipophilic compounds, will pass into breast milk, although to a variable extent. Breast feeding is therefore not recommended following administration of these compounds.

Fertility

No data available.

4.7 Effects on ability to drive and use machines

Use of propranolol is unlikely to result in any impairment of the patients ability to drive or operate machinery. However, it should be taken into account that occasionally dizziness or fatigue may occur.

4.8 Undesirable effects

Propranolol is usually well tolerated and side effects are usually transient in nature, rarely necessitating withdrawal of the treatment. The most serious adverse effects encountered are congestive heart failure and bronchospasm in susceptible patients.

The frequencies of adverse events are ranked according to the following: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data).

Metabolism and nutrition disorders

Not known: Hypoglycaemia in children, including hypoglycaemia-linked seizures.

Psychiatric disorders

Rare: Visual hallucinations

Not known: Depression

Nervous system disorders

Common: Sleep disturbances

Rare: Paraesthesia, dizziness

Not known: Lassitude, insomnia, nightmares, psychiatric complications (psychoses, psychotic reactions and acute confusional states) and mood changes.

Cardiac disorders
Common: Bradycardia
Rare: Deterioration of heart failure
Not known: Hypotension, exacerbation of intermittent claudication, congestive heart failure, postural hypotension which may be associated with syncope, paraesthesia of the hands, Raynaud's phenomenon and precipitation of heart block.

Vascular disorders
Common: Cold extremities
Rare: Orthostatic hypotension

Respiratory, thoracic and mediastinal disorders
Rare: Bronchospasm in patient with a history of bronchospastic complaints.
Not known: Bronchospasm may occur in patients with bronchial asthma or a history of asthmatic complaints, sometimes with fatal outcomes. Also respiratory distress and laryngospasm.

Gastrointestinal disorders
Uncommon: Non-severe diarrhoea, nausea
Not known: Vomiting, flatulence

Skin and subcutaneous tissue disorders
Rare: Purpura, rash
Not known: Exacerbation of psoriasis, psoriasiform skin reactions, alopecia, dry eyes, skin rashes and conjunctival xerosis.

Haematological
Not known: Reduction of platelet adhesiveness, thrombocytopenia purpura, nonthrombocytopenia purpura.

An increase in antinuclear antibodies (ANA) has been observed but the clinical relevance is not clear.

Reproductive system and breast disorders
Not known: Isolated reports of impotence have been recorded.

Eye disorders
Not known: Visual disturbances, diminished vision

Ear and labyrinth disorders
Rare: Diminution and loss of hearing

General disorders and administration site conditions
Common: Fatigue

Gastrointestinal disturbances (anorexia, nausea, vomiting, diarrhoea, abdominal pain) are the most common adverse effects reported. Other less frequently reported adverse reactions are cold extremities and exacerbation of Raynaud's phenomenon, congestive heart failure, sleep disturbances including vivid dreams, dizziness, fatigue and bronchospasm. Rare cases of thrombocytopenia and purpura have been reported. Bradycardia and CNS symptoms including mood changes and hallucinations have been reported rarely.

Other adverse effects of unknown frequency include fatigue, loss of libido, tinnitus, conjunctivitis, pharyngitis, fever combined with aching and sore throat, urinary retention associated with repeated bouts of paroxysmal tachycardia and flushing of the face. Isolated reports of myasthenia gravis-like syndrome or exacerbation of myasthenia gravis have been reported.

Propranolol discontinuation should be considered if, according to clinical judgement, the well-being of the patient is adversely affected by any of the above reactions. Cessation of therapy with a beta-blocker should be gradual. In the rare event of intolerance, manifested as bradycardia and hypotension, the beta-blocker should be withdrawn and, if necessary treatment for overdosage instituted.

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://nzphvc.otago.ac.nz/reporting/

4.9 Overdose
Symptoms
The common signs to be expected in overdosage are bradycardia, hypotension, bronchospasm or acute cardiac failure.

Treatment
If overdosage occurs, in all cases therapy with propranolol should be discontinued and the patient observed closely. In addition the following therapeutic measures are suggested.

General treatment should include close supervision in a monitored environment (which may include treatment in an intensive care ward), the use of gastric lavage, activated charcoal and a laxative to prevent absorption of any drug still present in the gastrointestinal tract, the use of intravenous fluids to treat hypotension and shock.

Excessive bradycardia
Can be countered with atropine 1 to 2 mg intravenously (incrementally in 0.6mg doses) and/or a cardiac pacemaker. If necessary this may be followed by a bolus dose of glucagon 10 mg intravenously. If required this may be repeated or followed by an intravenous infusion of glucagon (1 to 10 mg/hour) depending on response. If no response to glucagon occurs, or if glucagon is unavailable, a beta-adrenoceptor stimulant such as isoprenaline (25 mcg initially) or orciprenaline (0.5 mg) may be given by slow intravenous injection, or dobutamine (2.5-10mcg/kg/min) by intravenous infusion may be given.

Cardiac Failure
Digitalisation and diuretics.

Hypotension
Vasopressors, e.g. noradrenaline or adrenaline (there is evidence that adrenaline is the drug of choice).

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: β-adreneroreceptor blocking agent, ATC code: C07AA05

Propranolol is a ß-andrenoreceptor blocking agent which is structurally related to other beta-blocking agents such as atenolol, pindolol and oxprenolol, differing from these compounds by substitution on the aromatic ring. Propranolol is a competitive antagonist at both the $beta_1$ and $beta_2$-adrenoreceptors. It has little intrinsic sympathomimetic activity. It has some membrane stabilising effect at concentrations exceeding 1-3mg/L, although such concentrations are rarely achieved during oral therapy. Competitive beta-andrenoreceptor blockade has been demonstrated in

man by a parallel shift to the right in the dose-heart rate response curve to beta-antagonists such as isoprenaline.

As with other beta-andrenoreceptor blocking medicines, propranolol has negative intropic effects and is therefore contraindicated in congestive heart failure.

Propranolol hydrochloride is a racemic mixture and the active form is the S (-) isomer of propanolol. With the exception of inhibition of the conversion of thyroxine to triiodothyronine it is unlikely that any additional ancillary properties possessed by R (+) propranolol, in comparison with the racemic mixture will give rise to different therapeutic effects.

The most important effect of propranolol hydrochloride is to reduce the influence of excessive sympathetic nervous stimulation on the heart. Pulse rate, force of cardiac contraction and cardiac output are all reduced, resulting in a significant reduction in myocardial oxygen demand, greater than the reduction in work. These effects singly or in combination, are of therapeutic value in several cardiovascular diseases. Propranolol reduces elevated blood pressure by an unknown mechanism. The drug also inhibits exercise induced tachycardia and this effect is related to plasma concentration. No correlation has been found between the plasma concentration and its antihypertensive effect.

The possible mechanism of the antianginal activity of propranolol hydrochloride appears to be due to a reduction in the left ventricular work and oxygen utilisation resulting from inhibition or cardiac sympathetic nerve stimulation. Serotonin antagonism has been demonstrated with propranolol hydrochloride. The therapeutic benefit of this property in centrally medicated disorders is uncertain.

5.2 Pharmacokinetic properties

Absorption

Propranolol is completely absorbed after oral administration and peak plasma concentrations occur 1 to 2 hours after dosing in fasting patients.

Distribution

Following intravenous administration the plasma half-life of propranolol is about 2 hours. Propranolol is widely and rapidly distributed throughout the body with highest levels occurring in the lungs, liver, kidney, brain and heart. Propranolol is highly protein bound (80 to 95%).

Biotransformation

The ratio of metabolites to parent medicine in the blood is lower than after oral administration. In particular 4-hydroxy propranolol is not present after intravenous administration.

Elimination

The liver removes up to 90% of an oral dose with an elimination half-life of 3 to 6 hours.

Special patient populations

Since the half-life may be increased in patients with significant hepatic or renal impairment, care should be taken when starting treatment and selecting the initial dose.

5.3 Preclinical safety data

No information available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The excipients of Drofate are:

- Lactose monohydrate
- Corn starch
- Sodium starch glycollate
- Magnesium stearate
- Povidone

Drofate 10mg tablets also contain the colourants:

- Sunset Yellow (CI15985)
- Quinoline Yellow (CI47005)

Drofate 40mg tablets also contain the colourants:

- Sunset Yellow (CI15985),
- Quinoline Yellow (CI47005)
- Brilliant Blue (CI42090)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Shelf life: 36 months from the date of manufacture.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

White HDPE bottles with white PP CR Caps containing 90 or 100 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

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

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Teva Pharma (New Zealand) Limited
PO Box 128 244
Remuera
Auckland 1541
Telephone: 0800 800 097

9. DATE OF FIRST APPROVAL

7 September 2017

10. DATE OF REVISION OF THE TEXT

4 June 2021

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.4, 4.5, 4.8	Safety information revised in accordance with Teva CCSI No. 172/03/01/17