PRODUCT INFORMATION

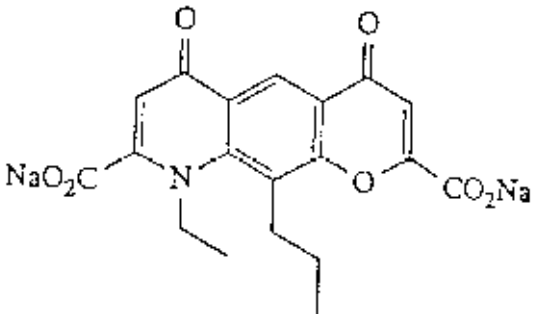
TILADE CFC-FREE

NAME OF THE MEDICINE

nedocromil sodium

DESCRIPTION

Tilade CFC-Free contains nedocromil sodium as a suspension in a non-CFC propellant, 1,1,1,2,3,3,3-heptafluoropropane (HFA-227). Other excipients include povidone, macrogol 600 and menthol.



CAS number: 69049-74-7[4]

Nedocromil sodium (Disodium 9-ethyl-6,9-dihydro-4,6-dioxo-10-propyl-4H-pyrano-(3,2-g)quinoline-2,8-dicarboxylate).

PHARMACOLOGY

Nedocromil sodium inhibits the release of inflammatory mediators from a variety of cell types occurring in the lumen and in the mucosa of the bronchial tree. Laboratory experiments have shown that nedocromil sodium prevents the release of inflammatory chemotactic and smooth muscle contracting mediators which are preformed or derived from arachidonic acid metabolism by both the lipoxygenase and cyclo-oxygenase pathways in a range of human and animal leucocytes. In the Ascaris suum sensitised monkey subjected to bronchial challenge with specific antigen, nedocromil sodium provides protection against changes in airways resistance and lung compliance. Nedocromil sodium prevents the release of mediators such as histamine, LTC_4 and PGD_2 from the cellular population of the chronically inflamed bronchus. There is growing evidence that these mediators are important also in lung disease in man, and this additional activity may be expected to give nedocromil sodium extended scope in the management of bronchial asthma in which inflammation, allergy and bronchial hyper-responsiveness are significant physiological factors.

Pharmacokinetics

After inhalation, nedocromil sodium is deposited throughout the respiratory tract, from which about 5% of the dose is absorbed. By the nature of inhalation dosing, much of the delivered dose is swallowed directly or subsequently upon mucociliary clearance from the large airways. A small amount of nedocromil sodium is subsequently absorbed from the gastrointestinal tract. Since the absorption rate constant from the respiratory tract is slower

than the elimination rate constant in bile and urine, the terminal half life (1.5 - 2 hours) reflects the rate of lung absorption. The drug is cleared sufficiently rapidly from the circulation so that successive doses according to the recommended regimen do not accumulate.

Nedocromil sodium is bound (up to 89%) reversibly to human plasma proteins and to a lesser extent in animals. It is not metabolised in man or in animals. It is excreted unchanged in the urine (in man, approximately 70%) and in faeces (in man, approximately 30%). While the plasma concentration falls rapidly (i.e. to 10% of peak levels in 8 hours) and urinary excretion is 90% complete within 12 hours, faecal elimination may take up to 3 days to be completed.

The pharmacokinetic profile of nedocromil is similar in healthy volunteers and in patients with bronchial asthma.

Clinical Trials

In the management of asthma, Tilade CFC-Free improves pulmonary function, reduces the frequency and severity of attacks and reduces bronchospasm, cough and bronchial hyper-reactivity.

In challenge studies, a single dose of Tilade CFC-Free afforded protection against bronchospasm provoked by exercise, inhaled allergens, cold air, atmospheric pollutants and other irritants. Continuous administration of Tilade CFC-Free reduces the bronchial hyper-reactivity seen in many patients with reversible obstructive airways disease.

INDICATIONS

Tilade CFC-Free is indicated for the prophylactic treatment of mild to moderate persistent asthma in adults and frequent episodic asthma in children aged over two years, and for the prevention of bronchospasm provoked by exercise, cold air, inhaled allergens, atmospheric pollutants and other irritants.

CONTRAINDICATIONS

Known hypersensitivity to nedocromil sodium, or any of the other excipients.

PRECAUTIONS

Tilade CFC-Free contains a hydrofluoroalkane propellant (apaflurane). In animal studies, narcosis and sensitisation to the arrhythmogenic effects of adrenaline were observed following inhalation of apaflurane at high exposure concentrations. The potency of the cardiac sensitisation was less than that of trichlorofluoromethane (CFC-11). In humans, apaflurane is absorbed into the circulation following inhalation administration, although the plasma concentrations are low and elimination is rapid. Excessive use of Tilade CFC-Free should be avoided as this carries a potential hazard, both from the propellant as well as from overdosage of the active drug in the formulation.

Tilade CFC-Free is intended for regular prophylactic treatment and not for symptomatic relief.

Tilade CFC-Free should not be used in preference to steroids in patients with severe rapidly worsening asthma. The role of Tilade CFC-Free in stable asthmatics controlled with inhaled steroids to enable a reduction of steroid dose is not clear and if this is planned, the steroid reduction should be gradual and the patient closely monitored. Tilade CFC-Free is not a bronchodilator and should not be used as an alternative to bronchodilator although its regular use may reduce the need for bronchodilators.

Information for patients

Tilade CFC-Free should not be used for the relief of an acute attack of bronchospasm.

Regular use of Tilade CFC-Free is usually required. Patients should not stop Tilade CFC-Free treatment abruptly unless directed to by a doctor.

Good inhaler technique is essential and should be checked frequently. The use of a spacer device may be helpful to facilitate inhalation of the drug by those patients who are unable to use the metered dose inhaler efficiently.

Use in pregnancy

Pregnancy Category B1

Small amounts of nedocromil sodium are known to cross the placenta but without effect in animals. Animal studies have not shown any teratogenic or other adverse effects on reproductive parameters in mice, rats and rabbits dosed subcutaneously with nedocromil sodium at doses up to 100mg/kg/day. However as with all new medicines, caution should be exercised, especially during the first trimester of pregnancy.

Use in lactation

On the basis of animal studies and its physicochemical properties, it is considered that only negligible amounts of nedocromil sodium may pass into human breast milk. The concentrations of nedocromil sodium in milk of animals was very low but concentrations in human breast milk have not been established. Animal studies have indicated no adverse effect of nedocromil sodium in suckling newborn rats receiving the drug from the parent (dosed subcutaneously at 100mg/kg/day) or directly by subcutaneous injection (100mg/kg/day). There is no information to suggest that the use of nedocromil sodium by nursing mothers has any undesirable effects on the baby; however, the benefits to a nursing mother must be weighed against the potential risk to the child.

CarcinogenicityA two year inhalation study in rats and a 21 month dietary study in mice showed no evidence of carcinogenic activity of nedocromil sodium at doses up to 25 and 180 mg/kg/day respectively; systemic exposure at these doses (based on time weighted concentration of unbound drug in plasma) was about 20 times greater than that in humans receiving the maximum recommended dose.

Genotoxicity

Nedocromil showed no conclusive evidence of genotoxic activity in a standard battery of assays.

Interactions with other medicines

Tilade CFC-Free has been used in association with numerous other drugs in man including beta-adrenergic agonists; inhaled and oral corticosteriods; theophylline and other methylxanthines; and ipratropium bromide. No harmful interactions have been observed in humans or in animals.

In patients already receiving treatment for their asthma, Tilade CFC-Free may be given in addition to existing therapies and will in many cases provide added therapeutic benefit. Having established this benefit of Tilade CFC-Free, it may be possible to eliminate or reduce concomitant therapy.

ADVERSE EFFECTS

Few side effects have been reported, principally headache (5%) and upper gastrointestinal symptoms (nausea, vomiting, dyspepsia and abdominal pain) (<5%). These are usually mild and transient.

In common with other inhaled medications, Tilade CFC-Free may produce cough, pharyngitis or bronchospasm. Unusual or unpleasant taste may occur.

Adverse experiences reported among patients treated with Tilade or Tilade CFC-Free during comparative clinical trials in adults, or long-term treatment in children, are shown in the following table. Included are all adverse experiences occurring with an incidence of 1% or greater in any treatment group, and judged to be treatment related[3].

The paediatric data presented below have all been generated from a single uncontrolled open-label long-term safety study. A comparison with the overall reporting in this trial shows that the percentage of adverse events rated as " related to test drug " is unusually high (approximately 30% of the total) compared to previous findings including paediatric studies on nedocromil sodium where this rate was 1 - 10%.

Preferred term	TILADE CFC-FREE		TILADE	
	Adult Patients (n=800) %	Paediatric Patients (n=213) %	Adult Patients (n=194) %	Paediatric Patients (n=0) %
Cough increased	8.25	28.2	5.7	-
URTI	-	25.8	-	-
Fever	-	15.0	-	-
Pharyngitis	3.75	14.6	5.2	-
Headache	-	16.9	-	-
Bronchospasm	1.25	14.6	2.1	-
Rhinitis	-	9.9	-	-
Taste of treatment	3.13	8.0	-	-
Allergic reaction	-	7.5	-	-
Otitis media	-	7.0	-	-
Abdominal pain	-	7.0	-	-
Vomiting	-	6.6	-	-
Nausea	-	5.6	-	-
Urticaria	-	5.2	-	-
Conjunctivitis	-	3.8	-	-
Infection Viral	-	2.8	-	-
Chest pain	-	3.3	1.5	-
Dysphonia	-	2.3	-	-
Diarrhoea	-	2.3	-	-
Earache	-	2.3	-	-
Influenza-like syndrome	-	1.9	-	-
Dizziness	-	1.9	-	-
Fatigue	-	1.9	-	-
Eczema	-	1.4	-	-
Rash erythematous	-	1.4	-	-
Gastroenteritis	-	1.4	-	-

Preferred term	TILADE CFC-FREE		TILADE	
	Adult Patients (n=800) %	Paediatric Patients (n=213) %	Adult Patients (n=194) %	Paediatric Patients (n=0) %
Sputum increased	-	1.4	-	-
Dyspnoea	-	-	1.5	-
Mouth dry	-	-	1.5	-

Dash (-) represents an incidence of less than 1%

DOSAGE AND ADMINISTRATION

Adults (including the elderly) and children over 2 years of age:

The recommended initial dosage is two actuations (each yielding 2mg of nedocromil sodium) four times daily. Some patients who have demonstrated a good response to therapy and whose asthma is stable may be able to reduce the dose to two actuations twice daily. This may take more than one week of regular use.

The efficacy of Tilade CFC-Free in children under 2 years of age has not been established.

Tilade CFC-Free, in a single dose of two actuations (4 mg) a few minutes before exposure, affords protection for several hours against bronchospasm provoked by exercise, cold air, inhaled allergens, atmospheric pollutants and other irritants.

Most patients will benefit from the consistent use of a spacer device with their metered dose inhaler (MDI or puffer), particularly those with poor inhaler technique. Use of a spacer will also decrease the amount of drug deposited in the mouth and back of the throat, and therefore, reduce the incidence of local side effects such as mouth and throat irritation and hoarse voice.

In those people using a spacer, a change in formulation of the drug used, or a change in the make of spacer may be associated with alterations in the amount of drug delivered to the lungs. The clinical significance of these alterations is uncertain. However, in these situations, the person should be monitored for any loss of asthma control.

The patient should be instructed to closely follow the instructions for the proper use of the spacer.

Static on the walls of the spacer may cause variability in drug delivery. Patients should be instructed to wash the spacer in warm water and detergent and allow it to dry without rinsing or drying with a cloth. This should be performed before initial use of the spacer and at least monthly thereafter

OVERDOSAGE

Animal studies have not shown evidence of toxic effects of nedocromil sodium even at extremely high dosage, nor have extended human studies revealed any safety hazard with the drug.

Overdosage is therefore unlikely to cause problems. However, if overdosage is suspected, treatment should be supportive and directed to the control of the relevant symptoms.

PRESENTATION AND STORAGE CONDITIONS

Metered dose pressurised aerosol (2 mg/actuation) containing 112 metered doses Menthol flavoured. An additional mouthpiece has been supplied to assist in the cleaning and maintenance of the Tilade CFC-Free Inhaler.

Store below 30^{o}C away from direct sunlight but do not freeze. The canister is pressurised and must not be punctured or burnt even when empty.

NAME AND ADDRESS OF SPONSOR

Sanofi-aventis australia pty ltd

12-24 Talavera Road

Macquarie Park NSW 2113

POISON SCHEDULE

S4

DATE OF APPROVAL

Date of TGA approval: 21 September 1995

Date of most recent amendment: 17 November 2008