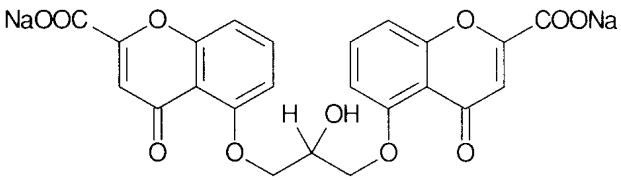
PRODUCT INFORMATION

INTAL CFC-FREE INHALER AND INTAL FORTE CFC-FREE INHALER

NAME OF MEDICINE

Sodium Cromoglycate for Oral Inhalation.



$C_{23}H_{14}Na_2O_{11}$ Mol Wt. 512.3

CAS No. [15826-37-6]

Sodium cromoglycate is a white crystalline odourless powder. It is soluble in 20 parts water at 20ºC. Chemically it is the disodium salt of 1, 3-bis (2 carboxychromon 5-yloxy) -2-hydroxypropane.

DESCRIPTION

INTAL is a metered dose inhaler containing sodium cromoglycate as a suspension in the propellant 1,1,1,2,3,3,3,-heptafluoropropane (HFA-227), a non CFC (chlorofluorocarbon) propellant. Other excipients include povidone and macrogol 600.

PHARMACOLOGY

Sodium cromoglycate inhibits the release from sensitised cells of mediators of the allergic reaction. In the lung this inhibition of mediator release prevents both the immediate and late asthmatic response to immunological and other stimuli. It has no effect on normal immunological defence mechanisms and no intrinsic bronchodilator or antihistamine activity.

When the compound is administered by inhalation up to 10% of the dose is absorbed in the lung. The remainder is either exhaled, deposited in the oropharynx, or is swallowed and eliminated via the alimentary tract. Approximately 1% of the inhaled dose is absorbed in the gastrointestinal tract. The absorption rate in the lungs is slower than the elimination rate (elimination half life 1.5-2 hours). A single dose of 2 x 5mg in healthy subjects was associated with a mean maximum plasma concentration of 6.2ng/mL (sd 4.1). Sodium cromoglycate is moderately and reversibly bound to plasma proteins (approximately 65%) and is not metabolised in humans. It is excreted unchanged in both urine and bile in approximately equal proportions.

CLINICAL TRIALS

An exercise challenge study was performed in 16 mild to moderate paediatric and adult asthmatics who had a history of exercise-induced bronchospasm. The protective effect of Intal Forte CFC-Free was compared with that of Intal Forte CFC formulation and placebo. For both the overall population and the children subgroup, there was a statistically significant

difference between the percent decrease in FEV_1 for Intal Forte CFC-Free and Intal Forte CFC when compared with placebo ($p<0.05$) and no statistically significant difference between Intal Forte CFC-Free and Intal Forte CFC formulation. Therefore it can be concluded that a clinically significant protection against exercise induced asthma, comparable to that seen with Intal Forte CFC formulation, can be achieved with Intal Forte CFC-Free in adult as well as in paediatric populations.

A comparative study was conducted to assess the safety of Intal Forte CFC-Free in a population of 184 asthmatic children over a period of 4 weeks and to determine if there were any adverse effects following changeover from Intal Forte CFC formulation to Intal Forte CFC-Free. Pulmonary function tests and other parameters used to monitor asthma control improved during the baseline period and remained stable when the patients were switched to Intal Forte CFC-Free. This finding supports the use of Intal Forte CFC-Free as a safe and effective alternative to Intal Forte CFC formulation.

Preclinical Data

INTAL CFC-free formulations contain a hydrofluoroalkane (HFA-227) propellant. In animal studies, HFA-227 has been shown to have no significant pharmacological effects, except at high exposure concentrations when narcosis and a relatively weak sensitisation to the arrhythmogenic effects of catecholamines were found. The potency of the cardiac sensitisation was less than that of trichloromethane (CFC-11). Although large doses of CFC propellants have been reported in animals to produce cardiac arrhythmias and sensitise their hearts to adrenaline-induced arrhythmia, data in humans are limited. Following inhalation of the maximum recommended dose of INTAL in humans, the plasma concentrations of the propellant were quite low. Excessive use of INTAL should, however, be avoided as this carries a potential hazard, both from the propellant as well as from overdosage of the active therapeutic agent contained in the formulation.

INDICATIONS

The prophylactic treatment of bronchial asthma, including the prevention of exercise induced bronchospasm.

CONTRAINDICATIONS

Hypersensitivity to sodium cromoglycate or any excipients of the formulation.

PRECAUTIONS

Intal formulations are not intended for the relief of an acute attack of bronchospasm.

Severe anaphylactic reactions can occur extremely rarely after sodium cromoglycate administration.

Patients may experience cough and/or bronchospasm following administration of Intal formulations. Some patients who develop bronchospasm may not be able to continue administration despite prior bronchodilator administration. Rarely, severe bronchospasm has been encountered.

In those cases where reduction of steroid treatment is attempted in patients receiving sodium cromoglycate, the patient must be carefully supervised while the steroid dose is reduced in a stepwise fashion. If possible, peak flow monitoring should be continued during such reductions and patients should be given instructions about what action to take if deterioration of asthma symptoms occurs.

Treatment with Intal formulations should be discontinued if an eosinophilic pneumonia appears

If an Intal formulation is to be withdrawn, the dosage should normally be reduced gradually over a period of a week, to avoid exacerbation of asthma. Symptoms of asthma may recur, following withdrawal of treatment.

For maintenance treatment of asthma, Intal formulations are essentially prophylactic and must be taken regularly to achieve benefit. (see Dosage and Administration)

Fertility

There was no evidence of impaired fertility in laboratory studies conducted subcutaneously in rats at doses of 175mg/kg/day in males and 100mg/kg/day in females.

Use in pregnancy

(Category B1) Intal may be assumed to have been taken by a large number of pregnant women and women of childbearing age without any signs of disturbance of the reproductive process, in the form of an increased frequency of malformations or other direct or indirect harmful effects on the foetus, having been observed to date. As with all medication, caution should be exercised, especially during the first trimester of pregnancy. However use in pregnancy should only occur if the benefit to the mother outweighs the potential risk to the foetus.

Use in lactation

Sodium cromoglycate passes into human breast milk, and its safety in infants has not been established. The drug, therefore, is not recommended for nursing mothers unless the expected benefit outweighs any potential risk.

Carcinogenicity

Long term studies of sodium cromoglycate in mice (12 months intraperitoneal administration at doses up to 150mg/kg three days per week), hamsters (intraperitoneal administration at doses up to 52.6mg/kg three days per week for 15 weeks followed by 17.5mg/kg three days per week for 37 weeks), and rats (18 months subcutaneous administration at doses up to 75mg/kg six days per week) showed no neoplastic effects.

Genotoxicity

Sodium cromoglycate was not genotoxic in assays for gene mutations and chromosomal damage.

Interaction with other medicines

No specific drug-drug interaction studies have been undertaken with Intal CFC-Free formulations. However, no evidence of interaction with other drugs has been observed with the CFC formulation.

ADVERSE EFFECTS

Mild throat irritation, coughing and transient bronchospasm may occur. As with other inhalation therapy, paradoxical bronchospasm may occur immediately after administration. The product should be discontinued and alternative treatment instituted. Hypersensitivity reactions, including angioedema, bronchospasm, hypotension and collapse, have been reported extremely rarely.

Adverse experiences reported among patients treated with Intal Forte or Intal Forte CFC-free during comparative clinical trials 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.

Preferred term	INTAL FORTE CFC-free		INTAL FORTE	
	Adult Patients (n=373)	Paediatric Patients (n=122)	Adult Patients (n=188)	Paediatric Patients (n=62)
	%	%	%	%
Cough increased	2.1	4	2.1	4.8
Pharyngitis	1.3	-	1.6	4.8
Bronchospasm	-	3.3	-	-
Taste of treatment	0.3	2.5	0.5	6.5
Fever	-	1.6	-	1.6
Nausea	0.3	1.6	-	1.6
Emotional lability	-	1.6	-	-
Abdominal pain	-	1.6	-	-

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

The following events have been reported very rarely, but a causal association with sodium cromoglycate has not been established: headache; abdominal pain and diarrhoea; arthralgia and myalgia; urticaria and skin rashes.

Very rare cases of eosinophilic pneumonia have been reported.

DOSAGE AND ADMINISTRATION

Patients vary in their response to INTAL CFC-Free formulations.

Intal (1mg) CFC-Free: Adults and Children: two inhalations of the aerosol four times daily. The suggested dosage regimen is two inhalations on retiring at night and on waking in the morning and at intervals of 4 to 6 hours. Additional doses before exercise may be taken. Prime the inhaler with four actuations prior to first use. If the inhaler is not used for more than 2 days, re-priming of the inhaler with four actuations is advised.

Intal Forte (5mg) CFC-Free: The recommended initial dosage of INTAL FORTE (5mg) CFC-Free is two inhalations twice daily. In some patients with more severe asthma, or during periods of severe challenge, an increased dosage of up to four inhalations four times daily may be required to achieve optimal control. To prevent asthmatic symptoms associated with exercise, a dose of two to four inhalations 5-10 minutes prior to exercise is recommended.

Prime the inhaler with four actuations prior to first use. Re-priming of the inhaler is not required where periods of non-use are between zero and two days (ie. less than 48 hours). Two re-priming actuations are required after periods of non-use of between three and seven days (ie. more than 48 hours). Beyond seven days of non-use, re-priming of the inhaler is accomplished with four actuations, as per the original priming instructions.[2]

The importance of regular washing of the Intal CFC-Free mouthpiece should be impressed upon the patient. The propellant used in Intal CFC-Free formulations is more prone to cause blockage, which may be prevented by washing the mouthpiece every night according to the enclosed leaflet instructions, and alternating daily with the spare mouthpiece provided.

[2] REP/06577v1 “Determination of priming, Re-priming and Loss of Prime Characteristics for Intal 1mg HFA-227 Metered Dose Inhalers” 31 July 2002.

Maintenance Treatment

Maintenance dosage should be individually assessed. Patients should be warned against suddenly discontinuing therapy when symptoms have been partially or completely controlled by INTALCFC-Free formulations.

Since the therapy is essentially prophylactic it is important to continue therapy in those patients who benefit. If it is necessary to withdraw this treatment it should be done progressively over one week. Symptoms of asthma may recur. (see Precautions)

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

There have been no reported cases in humans of overdosage of the drug. Symptomatic treatment is recommended should overdosage occur.

PRESENTATION AND STORAGE CONDITIONS

INTAL (1mg) CFC-Free: Metered dose pressurised aerosol delivering 200 actuations after initial priming. Each actuation contains sodium cromoglycate BP 1.0mg.

INTAL FORTE (5mg) CFC-Free: Metered dose pressurised aerosol delivering 112 actuations after initial priming. Each actuation contains sodium cromoglycate BP 5.0 mg.

An additional mouthpiece has been supplied in each pack, to assist in the cleaning and maintenance of the CFC-Free Inhaler.

Store below 30 degrees Celsius, in a dry place away from direct sunlight.

NAME AND ADDRESS OF THE SPONSOR

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Macquarie Park NSW 2113

DATE OF APPROVAL

Date of TGA approval: 31 March 2003

Date of amendment: 08 March 2016