IMIGRAN™

Sumatriptan Injection

QUALITATIVE AND QUANTITATIVE COMPOSITION

Pre-filled syringes containing 6 mg of sumatriptan base as the succinate salt in an isotonic solution (total volume: 0.5 mL). An auto-injector is available.

PHARMACEUTICAL FORM

IMIGRAN injection is a clear, colourless to pale yellow liquid, practically free from particles.

CLINICAL PARTICULARS

Indications

IMIGRAN injection is indicated for the acute relief of migraine attacks with or without aura, including the acute treatment of migraine attacks associated with the menstrual period in women.

IMIGRAN injection is also indicated for the acute treatment of cluster headache.

Dosage and Administration

IMIGRAN should not be used prophylactically. The recommended dose of IMIGRAN should not be exceeded.

It is advisable that IMIGRAN be given as early as possible after the onset of a migraine headache or associated symptoms such as nausea, vomiting or photophobia. It is equally effective at whatever stage of the attack it is administered.

The efficacy of IMIGRAN is independent of the duration of the attack when starting treatment. Administration during a migraine aura prior to other symptoms occurring may not prevent the development of a headache.

IMIGRAN injection should be injected subcutaneously using an auto-injector.

Patients should be advised to observe strictly the instruction leaflet for the IMIGRAN auto-injector, especially regarding the safe disposal of syringes and needles.

Populations

- **Adults**

Migraine

The recommended dose of IMIGRAN injection is a single 6 mg subcutaneous injection.

If a patient does not respond to the first dose of IMIGRAN, a second dose should not be taken for the same attack. IMIGRAN injection may be taken for subsequent attacks.

If the patient has responded to the first dose, but the symptoms recur a second dose may be given in the next 24 hours, provided that there is a minimum interval of 1 hour between the two doses.

The maximum dose in 24 hours is two 6 mg injections (12 mg).

Cluster headache

The recommended dose of IMIGRAN injection is a single 6 mg subcutaneous injection for each cluster attack. The maximum dose in 24 hours is two 6 mg injections (12 mg) with a minimum interval of 1 hour between the two doses.

- **Children and Adolescents (under 18 years of age)**

IMIGRAN injection has not been studied in adolescents or children.

- **Elderly (over 65 years of age)**

Experience of the use of sumatriptan in patients aged over 65 years is limited. The pharmacokinetics do not differ significantly from a younger population, but until further clinical data are available, the use of IMIGRAN in patients aged over 65 years is not recommended.

Contraindications

– Hypersensitivity to any component of the preparation.

– IMIGRAN should not be given to patients who have had myocardial infarction or have ischaemic heart disease (IHD), Prinzmetal's angina/coronary vasospasm, peripheral vascular disease or patients who have symptoms or signs consistent with IHD.

– IMIGRAN should not be administered to patients with a history of previous cerebrovascular accident (CVA) or transient ischaemic attack (TIA).

– The use of IMIGRAN in patients with uncontrolled hypertension is contraindicated.

– IMIGRAN should not be administered to patients with severe hepatic impairment.

– The concomitant use of ergotamine or derivatives of ergotamine (including methysergide) is contraindicated (*see Interactions*).

– Concurrent administration of monoamine oxidase inhibitors (MAOIs) and IMIGRAN is contraindicated. IMIGRAN must not be used within two weeks of discontinuation of therapy with MAOIs.

Warnings and Precautions

IMIGRAN should only be used where there is a clear diagnosis of migraine or cluster headache.

IMIGRAN injection should not be given intravenously.

IMIGRAN is not indicated for use in the management of hemiplegic, basilar or ophthalmoplegic migraine.

Before treating with IMIGRAN, care should be taken to exclude potentially serious neurological conditions (e.g. CVA, TIA) if the patient presents with atypical symptoms or if they have not received an appropriate diagnosis for IMIGRAN use.

Following administration, IMIGRAN can be associated with transient symptoms including chest pain and tightness which may be intense and involve the throat (*see Adverse Reactions*). Where such symptoms are thought to indicate IHD, appropriate evaluation should be carried out.

IMIGRAN should not be given to patients in whom unrecognised cardiac disease is likely without a prior evaluation for underlying cardiovascular disease. Such patients include postmenopausal women, males over

40 and patients with risk factors for coronary artery disease. However, these evaluations may not identify every patient who has cardiac disease and, in very rare cases, serious cardiac events have occurred in patients without underlying cardiovascular disease.

IMIGRAN should be administered with caution to patients with controlled hypertension as transient increases in blood pressure and peripheral vascular resistance have been observed in a small proportion of patients.

There have been rare post-marketing reports describing patients with serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) following the use of a selective serotonin reuptake inhibitor (SSRI) and sumatriptan. Serotonin syndrome has been reported following concomitant treatment with triptans and serotonin noradrenaline reuptake inhibitors (SNRIs).

If concomitant treatment with IMIGRAN and an SSRI/SNRI is clinically warranted, appropriate observation of the patient is advised (*see Interactions*).

The concomitant administration of any triptan/5-HT_1 agonist with IMIGRAN is not recommended.

IMIGRAN should be administered with caution to patients with conditions that may affect significantly the absorption, metabolism or excretion of the drug, e.g. impaired hepatic (Child Pugh grade A or B; *see Pharmacokinetics – Special Patient Populations*) or renal function (*see Pharmacokinetics*).

IMIGRAN should be used with caution in patients with a history of seizures or other risk factors which lower the seizure threshold.

Patients with known hypersensitivity to sulphonamides may exhibit an allergic reaction following administration of IMIGRAN. Reactions may range from cutaneous hypersensitivity to anaphylaxis. Evidence of cross-sensitivity is limited, however, caution should be exercised before using IMIGRAN in these patients.

Overuse of acute headache treatments has been associated with the exacerbation of headache (medication overuse headache, MOH) in susceptible patients. Withdrawal of the treatment may be necessary.

Latex Allergy - The needle shield of the pre-filled syringe may contain dry natural latex rubber that has the potential to cause allergic reactions in latex sensitive individuals.

Interactions

There is no evidence of interactions with propanolol, flunarizine, pizotifen or alcohol.

Prolonged vasospastic reactions have been reported with ergotamine. As these effects may be additive, 24 hours should elapse before IMIGRAN can be taken following any ergotamine containing preparation. Conversely, ergotamine containing preparations should not be taken until six hours have elapsed following IMIGRAN administration.

An interaction may occur between IMIGRAN and MAOIs and concomitant administration is contraindicated (*see Contraindications*).

There have been rare post-marketing reports describing patients with serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) following the use of SSRIs and sumatriptan. Serotonin syndrome has also been reported following concomitant treatment with triptans and SNRIs (*see Warnings and Precautions*).

Pregnancy and Lactation

Pregnancy

Caution should be exercised by considering the expected benefit to the mother against possible risk to the foetus.

Post-marketing data from the use of sumatriptan during the first trimester in over 1,000 women are available. Although these data contain insufficient information to draw definitive conclusions, they do not point to an increased risk of congenital defects. Experience with the use of sumatriptan in the second and third trimester is limited.

Lactation

It has been demonstrated that following subcutaneous administration, sumatriptan is excreted into breast milk. Infant exposure can be minimised by avoiding breast-feeding for 24 hours after treatment.

Effects on Ability to Drive and Use Machines

Drowsiness may occur as a result of migraine or treatment with IMIGRAN.

Caution is recommended in patients performing skilled tasks, e.g. driving or operating machinery.

Adverse Reactions

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10000 to <1/1000) and very rare (<1/10000) including isolated reports. The data from clinical trials are estimates. It should be noted that the background rate in comparator groups was not taken into account. Post-marketing data refer to reporting rate rather than true frequency.

Clinical Trial Data

Nervous System Disorders

Common:	Dizziness, drowsiness, sensory disturbance including paraesthesia and hypoaesthesia.

Vascular Disorders

Common:	Transient increases in blood pressure arising soon after treatment. Flushing.

Respiratory, Thoracic and Mediastinal Disorders

Common:	Dyspnoea.

Gastrointestinal Disorders

Common:	Nausea and vomiting occurred in some patients but the relationship to sumatriptan is not clear.

Musculoskeletal and Connective Tissue Disorders

The following symptom is usually transient and may be intense and can affect any part of the body including the chest and throat:

Common:	Sensations of heaviness.

General Disorders and Administration Site Conditions

The most common side effects associated with treatment with IMIGRAN administered subcutaneously are:

Very common:	Transient injection site pain.
	Injection site stinging/burning, swelling, erythema, bruising and bleeding have also been reported.

The following symptoms are usually transient and may be intense and can affect any part of the body including the chest and throat:

Common:	Pain, sensations of heat or cold, pressure or tightness.

The following symptoms are mostly mild to moderate in intensity and transient:

Common:	Feelings of weakness, fatigue.

Investigations

Very rare:	Minor disturbances in liver function tests have occasionally been observed.

Although direct comparisons are not available, flushing, paraesthesia and sensations of heat, pressure, and heaviness may be more common after IMIGRAN injection.

Conversely, nausea, vomiting and fatigue appear to be less frequent with subcutaneous administration of IMIGRAN injection than with tablets.

Post-Marketing Data

Immune System Disorders

Very rare:	Hypersensitivity reactions ranging from cutaneous hypersensitivity to anaphylaxis.

Nervous System Disorders

Very rare:	Seizures, although some have occurred in patients with either a history of seizures or concurrent conditions predisposing to seizures there are also reports in patients where no such predisposing factors are apparent.
	Tremor, dystonia, nystagmus, scotoma.

Eye Disorders

Very rare:	Flickering, diplopia, reduced vision. Loss of vision (usually transient). However, visual disorders may also occur during a migraine attack itself.

Cardiac Disorders

Very rare:	Bradycardia, tachycardia, palpitations, cardiac arrhythmias, transient ischaemic ECG changes, coronary artery vasospasm,

	angina, myocardial infarction (*see Contraindications, Warnings and Precautions*).

Vascular Disorders

Very rare:	Hypotension, Raynaud's phenomenon.

Gastrointestinal Disorders

Very rare:	Ischaemic colitis.

Overdose

Symptoms and Signs

There have been some reports of overdosage with IMIGRAN injection.

Patients have received single injections of up to 12 mg subcutaneously without significant adverse effects. Doses up to 16 mg subcutaneously were not associated with side effects other than those mentioned.

Treatment

If overdosage occurs, the patient should be monitored for at least 10 hours and standard supportive treatment applied as required.

It is unknown what effect haemodialysis or peritoneal dialysis has on the plasma concentrations of sumatriptan.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

ATC Code

N02CC01.

Mechanism of Action

Pharmacotherapeutic group: Selective 5-HT_1 receptor agonists.

Sumatriptan has been demonstrated to be a selective vascular 5-hydroxytryptamine-1-(5-HT_1D) receptor agonist with no effect at other 5-HT receptor (5-$HT_{2–7}$) subtypes. The vascular 5-HT_1D receptor is found predominantly in cranial blood vessels and mediates vasoconstriction.

In animals, sumatriptan selectively constricts the carotid arterial circulation, but does not alter cerebral blood flow. The carotid arterial circulation supplies blood to the extracranial and intracranial tissues such as the meninges and dilatation and/or oedema formation in these vessels is thought to be the underlying mechanism of migraine in man. In addition, experimental evidence suggests that sumatriptan inhibits trigeminal nerve activity. Both these actions may contribute to the anti-migraine action of sumatriptan in humans.

Pharmacodynamic Effects

Clinical response begins 10 to 15 minutes following a 6 mg subcutaneous injection, 15 minutes following a 20 mg dose given by intra-nasal administration and around 30 minutes following a 100 mg oral dose or 25 mg rectal dose.

Sumatriptan is effective in the acute treatment of migraine including menstrually-associated migraine.

Pharmacokinetics

The pharmacokinetics of sumatriptan do not appear to be significantly affected by migraine attacks.

Absorption

Following subcutaneous injection sumatriptan has a high mean bioavailability (96%) with peak serum concentrations occurring in 25 minutes. Average peak serum concentration after a 6 mg subcutaneous dose is 72 nanograms/mL.

Distribution

Plasma protein binding is low (14 to 21%); the mean total volume of distribution is 170 litres.

Metabolism

The major metabolite, the indole acetic acid analogue of sumatriptan is mainly excreted in urine, where it is present as a free acid and the glucuronide conjugate. It has no known 5-HT_1 or 5-HT_2 activity. Minor metabolites have not been identified.

Elimination

The elimination half-life is approximately two hours. The mean total plasma clearance is approximately 1,160 mL/min and the mean renal plasma clearance is approximately 260 mL/min.

Non-renal clearance accounts for about 80% of the total clearance. Sumatriptan is eliminated primarily by oxidative metabolism mediated by monoamine oxidase A.

Special Patient Populations

- **Hepatic Impairment**

The effect of moderate hepatic disease (Child Pugh grade B) on the pharmacokinetics of subcutaneously administered sumatriptan has been evaluated. There were no significant differences in the pharmacokinetics of subcutaneously administered sumatriptan in moderately hepatically impaired subjects compared with healthy controls (*see Warnings and Precautions*).

Pre-Clinical Safety Data

Carcinogenesis, mutagenesis

Sumatriptan was devoid of genotoxic and carcinogenic activity in *in vitro* systems and animal studies.

Reproductive toxicology

In a rat fertility study, oral doses of sumatriptan resulting in plasma levels approximately 150 times those seen in man after a 6 mg subcutaneous dose were associated with a reduction in the success of insemination.

This effect did not occur during a subcutaneous study where maximum plasma levels achieved approximately 100 times those in man by the subcutaneous route.

Pregnancy and lactation

No teratogenic effects have been seen in rats or rabbits, and sumatriptan had no effect on the post-natal development of rats.

When administered to pregnant rabbits throughout the period of organogenesis, sumatriptan has occasionally caused embryolethality at doses that were sufficiently high to produce maternal toxicity.

PHARMACEUTICAL PARTICULARS

List of Excipients

Sodium chloride
Water for injection
Nitrogen

Incompatibilities

None reported.

Shelf-Life

The expiry date is indicated on the packaging.

Special Precautions for Storage

IMIGRAN injection should be stored below 30°C, protected from light.

Nature and Contents of Container

A syringe, with an integrated needle, which is designed to be disposable, consists of the following components:

– Glass syringe barrel, Type I glass

– Stainless steel needle cannula

– Natural rubber needle shield

– Chlorobutyl rubber plunger stopper

All the above components are received pre-sterilised from the suppliers.

The pre-filled syringes should be used in conjunction with an auto-injector.

Instructions for Use/Handling

Patients should be advised to pay strict attention to the instruction leaflet for IMIGRAN injection, especially regarding the safe disposal of needles and syringes.

Needles and syringes may be hazardous and should be disposed of safely and hygienically.

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[GlaxoSmithKline logo]

IMIGRAN™
Glaxopen

Patient instruction leaflet

How to use the Glaxopen
Instructions for use of the Glaxopen Self-lnjector System

The Glaxopen is designed for use with only a medicine prescribed for you by your doctor called lmigran Injection. This leaflet shows you how to load the Glaxopen and how to use it to give a dose of Imigran Injection.

Please read this leaflet carefully before using the injection system.

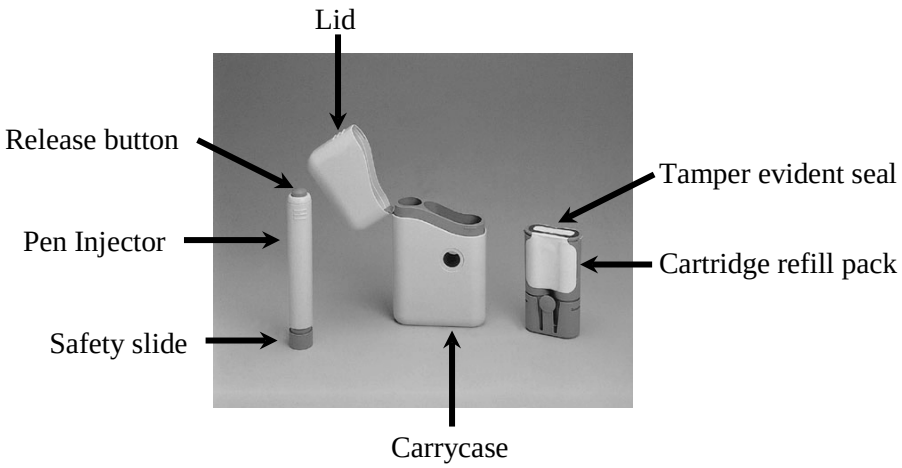
Each Glaxopen treatment pack comes with a carrycase, which contains the pen injector and a cartridge refill pack, which contains two syringe cartridges.

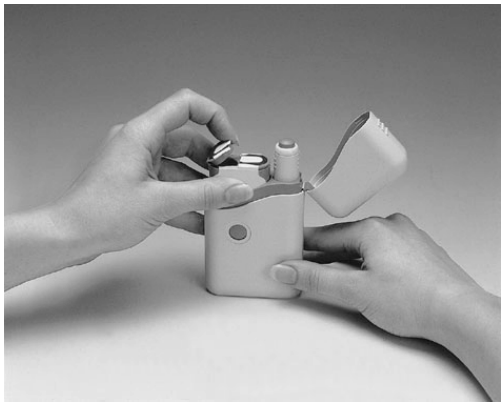
The cartridge refill pack can be supplied alone for future prescriptions.

Do not load the Glaxopen until you are ready to give the injection.

Description of the Glaxopen parts

Use the photo to help you identify the different parts of the Glaxopen.

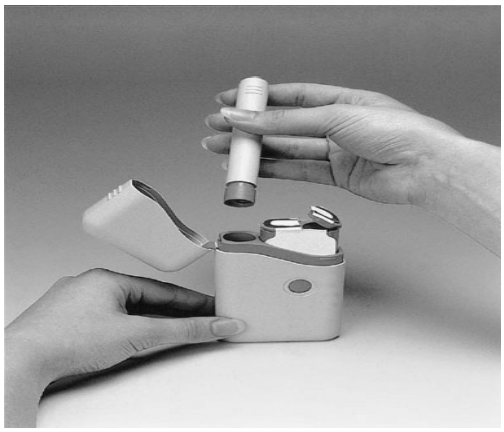




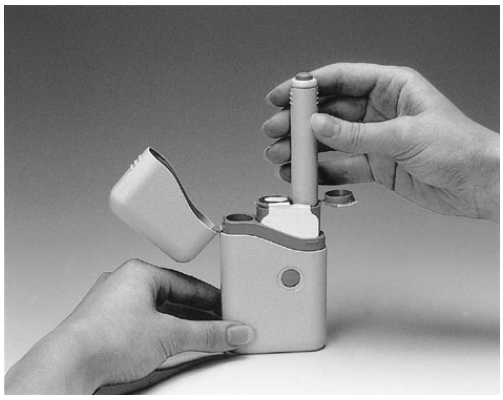
How to give an injection using the Glaxopen

1. Open the carrycase lid.

2. Tear off the tamper evident seal from one of the cartridges and open lid. If the tamper evident seal has been broken previously, do not use that syringe cartridge.



3. Take out the pen injector from the carrycase. Check that the White Rod is not sticking out beyond the end of the Pen. If it is sticking out, place the pen back inside the carrycase, push firmly and the rod should click into place. The pen is now ready for use

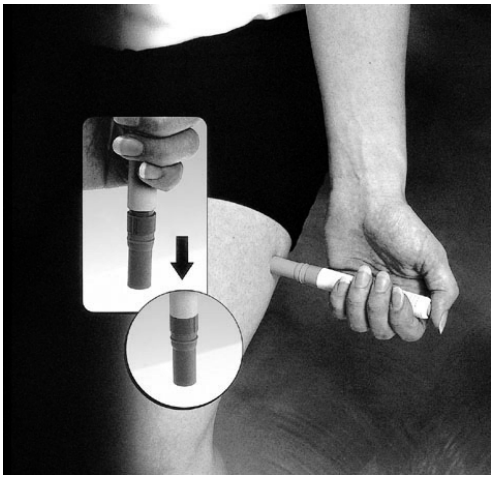


4. Push the pen firmly into the open cartridge pack and gently screw it clockwise (about half a turn) until it will twist no further.

5. Keep your finger away from the blue release button, pull the pen out of the cartridge pack. You may have to pull quite hard to do this. A safety catch stops accidental injection before you are ready.

6. The loaded pen is now ready for immediate use.

Do not try to put the loaded pen back into the carrycase until after you have used the injection, or the needle may be damaged and the pen will not inject correctly.

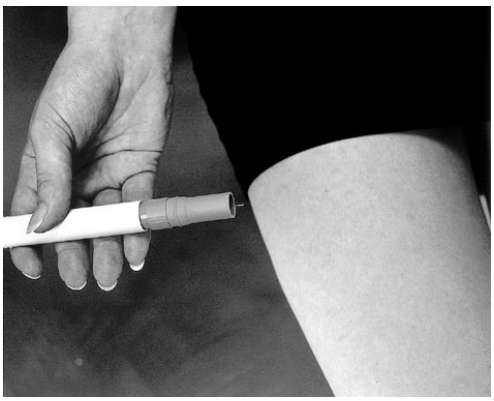


To give injection

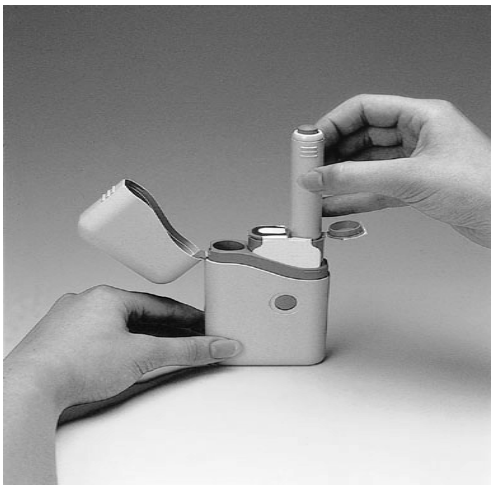
7. Holding the pen comfortably by the grey barrel, press the nose end firmly against an area of clear skin – usually the outer thigh area. The safety catch is overcome by pushing the grey section down as far as it will go.

8. Hold the pen firmly and press the blue release button at the top of the pen. Count slowly to 10 keeping the pen very still and the release button depressed.

Do not take the pen away from the skin too soon or some of the injection may be wasted.



9. After the full 10 seconds, carefully lift the pen from the skin, do not touch the exposed needle point.

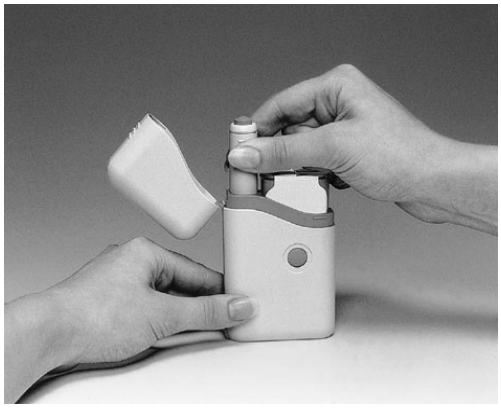


10. Return the used cartridge syringe to the empty space in the cartridge pack straight away.

11. Push the pen down into the cartridge pack as far as it will go. Unscrew the pen by twisting it anti-clockwise (about half a turn) until it comes away.

12. Withdraw the pen from the cartridge pack and close the lid over the used syringe cartridge.

    The white plunger rod is visible, showing that the pen device has been used.



To reactivate the Glaxopen mechanism

13. Put the pen to the carrycase holder, and push it down as far as it will go. It will click into place. The pen is then ready for use next time.

14. Close the lid of the case until you need to use the next syringe cartridge. When you have used both cartridges, you will need to remove and replace the cartridge refill pack.

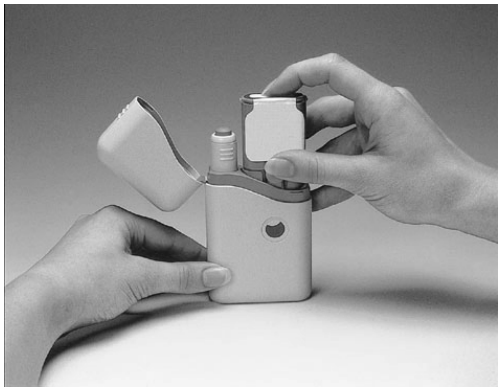
To remove the used cartridge pack

When both the doses have been used, the cartridge pack must be removed for disposal.

15. Hold the carrycase and press the two locating buttons between the thumb and forefinger.

16. Gently pull out the used cartridge pack with the other hand.

Ask your pharmacist how to dispose of medicines no longer required. This will help to protect the environment.



To load a new cartridge refill pack into the carrycase

Further dose of Imigran injection may be supplied in a cartridge refill pack.

17. Open the lid of the carrycase- the pen injector is already in place

18. Push the cartridge refill pack into the carrycase, pressing the blue locating buttons on either side so it slides in smoothly.

19. The refill cartridge pack is correctly sited when the blue locating buttons show through the holes on either side of the case.

20. You can keep your cartridge pack safely in the carrycase until you need to give yourself an injection.

Always keep your injections in the case provided to protect them from the light.

Store below 30°C.

Keep this medicine in a safe place, and out of the reach of children.

For further information, contact your Pharmacist or Doctor.

<GSK logo>

Manufactured by:

Glaxo Wellcome Operations
Barnard Castle, UK