NEW ZEALAND DATA SHEET

XERGIC

1. Product Name

Xergic 120 mg and 180 mg film coated tablet

2. Qualitative and Quantitative Composition

Each Xergic 120 mg film coated tablet contains 120 mg of fexofenadine hydrochloride.

Each Xergic 180 mg film coated tablet contains 180 mg of fexofenadine hydrochloride.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

Xergic 120 mg: Pink coloured, oval shaped, biconvex film coated tablets, debossed with “FXF” on one side and “120” on the other side.

Xergic 180 mg: Pink coloured, oval shaped, biconvex film coated tablets, debossed with “FXF” on one side and “180” on the other side.

4. Clinical Particulars

4.1 Therapeutic indications

Xergic 120 mg is indicated for the relief of symptoms associated with seasonal allergic rhinitis in adults and children aged 12 years or older.

Xergic 180 mg is indicated for the relief of symptoms associated with seasonal allergic rhinitis or urticaria in adults and children aged 12 years or older.

4.2 Dose and method of administration

Dose

Seasonal allergic rhinitis

120 mg or 180 mg once daily, when required.

Urticaria

180 mg once daily, when required.

Special risk groups

Studies in special risk groups (elderly, renally or hepatically impaired patients) indicate that it is not necessary to adjust the dose of fexofenadine hydrochloride in these patients.

Paediatric

There is currently not enough information available to recommend the use of fexofenadine hydrochloride 120 mg or 180 mg in children under the age of 12 years.

4.3 Contraindications

Xergic is contraindicated in patients with a known hypersensitivity to fexofenadine or any ingredient in the product (see section 6.1)

4.4 Special warnings and precautions for use

Studies in the elderly, patients with hepatic impairment and patients with cardiac disease exposed to fexofenadine through administration of terfenadine showed no statistically significant differences in pharmacokinetic parameters for fexofenadine when compared to those pharmacokinetic parameters in healthy individuals.

There is only limited data in the elderly and renally or hepatically impaired patients. Fexofenadine hydrochloride should still be administered with care in these special groups.

4.5 Interaction with other medicines and other forms of interaction

Since fexofenadine does not undergo hepatic biotransformation, it is unlikely to interact with medicines that rely upon hepatic metabolism.

Interaction studies with erythromycin and ketoconazole have shown that although the plasma levels of fexofenadine are increased 2–3 fold, there were no changes to QT interval and there were no changes to the incidence of any adverse events. The concentration of fexofenadine experienced by individuals during the interaction studies are well within the range experienced in acute and chronic dose-tolerance studies.

Animal studies have shown that the increase in plasma levels of fexofenadine observed after co-administration of erythromycin or ketoconazole, appears to be due to an increase in gastrointestinal absorption and either a decrease in biliary excretion or gastrointestinal secretion, respectively.

No interaction between fexofenadine and omeprazole was observed. However, the administration of an antacid containing aluminium and magnesium hydroxide gels 15 minutes prior to fexofenadine hydrochloride caused a reduction in bioavailability, most likely due to binding in the gastrointestinal tract. It is advisable to leave 2 hours between administration or fexofenadine hydrochloride and aluminium and magnesium hydroxide containing antacids.

Fruit juices such as grapefruit, orange and apple may reduce the bioavailability and exposure of fexofenadine. This is based on the results from 3 clinical studies using histamine induced skin wheals and flares coupled with population pharmacokinetic analysis. The size of wheal and flare were significantly larger when fexofenadine hydrochloride was administered with either grapefruit or orange juices compared to water. Based on the literature reports, the same effects may be extrapolated to other fruit juices such as apple juice. The clinical significance of these observations is unknown. In addition, based on the population pharmacokinetics analysis of the combined data from grapefruit and orange juices studies with the data from a bioequivalence study, the bioavailability of fexofenadine was reduced by 36%. Therefore, to maximize the effects of fexofenadine, it is recommended that fexofenadine tablets should be taken with water

4.6 Fertility, pregnancy and lactation

Category B2.

Reproductive toxicity of fexofenadine in animals was assessed through terfenadine exposure. Data from supporting pharmacokinetic studies, showing the extent of fexofenadine exposure, demonstrate that these studies are relevant to the assessment of fexofenadine hydrochloride. No evidence of

teratogenicity was observed in animal reproduction studies (rat and rabbit) when terfenadine was given at oral doses of up to 300 mg/kg/day throughout organogenesis which corresponds to levels of systemic fexofenadine exposure 4- and 32-fold higher, respectively, than those anticipated in clinical use. No effects on male or female fertility or perinatal or postnatal development were observed in terfenadine animal studies at non-maternally toxic doses.

There are no studies in pregnant women exposed to fexofenadine hydrochloride alone or through the administration of terfenadine. As with other medications, fexofenadine hydrochloride should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

There are no studies of fexofenadine hydrochloride in lactating women. Fexofenadine hydrochloride is not recommended for nursing women and should only be used if in the physician's judgement, the potential benefit outweighs the potential risk to the infant. There are no data on the content of human milk after administering fexofenadine hydrochloride. However, when terfenadine was administered to nursing mothers, fexofenadine was found to cross into human breast milk.

Exposure of rats to fexofenadine and terfenadine through the administration of terfenadine at doses of 150 and 300 mg/kg/day throughout pregnancy and lactation (corresponding to systemic exposure at levels (AUC) approximately 3- and 6-fold higher than those anticipated in clinical use) caused decreased pup weight gain and survival in offspring. The relative risks of these effects from terfenadine or fexofenadine are unknown. Effects on pups exposed to fexofenadine only during lactation are not known.

4.7 Effects on ability to drive and use machines

The incidence of drowsiness in controlled clinical seasonal allergic rhinitis trials was similar when comparing patients treated with fexofenadine and placebo. There was no dose-related increase in drowsiness.

On the basis of the pharmacodynamic profile and reported adverse events it is unlikely that fexofenadine hydrochloride tablets will produce an effect on the ability to drive or use machines. In objective tests, fexofenadine has been shown to have no significant effects on central nervous system function. This means that patients may drive or perform tasks that require concentration.

Although this medicine is unlikely to affect your ability to drive or operate machinery, a few people may be impaired and care should be taken.

4.8 Undesirable effects

Fexofenadine hydrochloride is generally well tolerated. In placebo controlled clinical trials involving seasonal allergic rhinitis and chronic idiopathic urticaria the most commonly reported adverse events were headache (> 3%), drowsiness, nausea, fatigue and dizziness (1-3%). The incidence of these events observed with fexofenadine hydrochloride was similar to that observed with placebo and no apparent dose trends were revealed in adverse events.

Events that have been reported during controlled clinical trials involving seasonal allergic rhinitis and chronic idiopathic urticaria patients with incidences less than 1% and similar to placebo, and have been reported rarely during post marketing surveillance, include: fatigue, insomnia, nervousness and sleep disorders or paroniria. In rare cases, rash, urticaria, pruritis and hypersensitivity reactions such as angiooedema, dyspnoea, chest tightness, flushing and systemic anaphylaxis have been reported. No notable dose effects on QTc were found.

Adverse events reported in placebo-controlled chronic idiopathic urticaria studies were similar to those reported in placebo-controlled seasonal allergic rhinitis studies.

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

Most reports of fexofenadine hydrochloride overdose contain limited information. However, dizziness, drowsiness and dry mouth have been reported. Single doses up to 800 mg and doses up to 690 mg twice daily for 1 month were studied in healthy subjects without the development of clinically significant adverse events.

Clinical signs of toxicity and effects on body weight or food consumption were not observed in acute toxicity studies in several animal species administered fexofenadine by oral lavage at doses of 2,000 mg/kg.

In the case of an overdose, standard measures to remove any unabsorbed drug should be employed. Symptomatic and supportive treatment is recommended. Haemodialysis is not an effective means of removing fexofenadine from plasma.

There has been no reported case of an acute overdose of fexofenadine hydrochloride.

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihistamine for systemic use, ATC code: R06AX26

Mechanism of action

Fexofenadine hydrochloride is the synthetic hydrochloride salt of fexofenadine, the carboxylic acid metabolite of terfenadine. It is an orally active non-sedating H_1-receptor antagonist and is effective for the relief of symptoms associated with seasonal allergic rhinitis (sneezing, rhinorrhea, pruritus and lacrimation).

Fexofenadine is the major metabolite of terfenadine in man and is largely responsible for the antihistaminic effect following the administration of terfenadine

Clinical efficacy and safety

The antihistaminic effects of fexofenadine have been demonstrated in animal systems *in vitro* and *in vivo*. Oral administration of fexofenadine to guinea pigs indicated that fexofenadine antagonised histamine-induced skin wheals in a dose-dependent manner. The antihistaminic effects of fexofenadine and terfenadine were also assessed in the isolated guinea pig ileum *in vitro*. Both drugs antagonised the contractile effects of histamine, however, fexofenadine was found to be a more selective histamine antagonist than terfenadine.

Fexofenadine inhibited antigen induced bronchospasm in sensitised guinea pigs and at high doses inhibited histamine release from peritoneal mast cells of the rat.

In laboratory animals, no anticholinergic or alpha-1-adrenergic receptor blocking effects were observed. Radiolabelled tissue distribution studies in rat indicated that fexofenadine did not cross the blood brain barrier.

Fexofenadine is not associated with significant ECG abnormalities. Studies have shown that fexofenadine does not affect the action potential and ion channel currents (I_K, I_{CA}, I_{Na}) in guinea pig or neonatal rat myocytes. The effect of fexofenadine on blocking a delayed rectifier potassium channel cloned from human heart was 583 times less potent than the same effect with terfenadine.

Doses of fexofenadine, ten times greater than the dose of terfenadine producing prolongation of QT_c intervals, do not prolong QT_c intervals in anaesthetised rabbits and conscious dogs.

An escalating acute-dose study demonstrated antihistaminic activity via skin wheal and flare inhibition at doses ranging from 10 to 800 mg, with maximum inhibition reaching a plateau at a dose of 130 mg. An escalating repeat-dose study demonstrated increasing skin flare inhibition at twice daily doses ranging from 20 to 690 mg. During both acute-dose and repeat-dose studies an antihistaminic effect was observed within one hour, achieving maximum effect within 2-4 hours and lasting a minimum of 12 hours. There is no evidence of tolerance to these effects after 28 days of dosing.

In dose-ranging studies, fexofenadine hydrochloride was shown to relieve the symptoms of seasonal allergic rhinitis, significantly reducing total symptom scores (including scores for nasal congestion, sneezing, rhinorrhea, itchy nose, palate and/or throat, and itchy, watery, red eyes) over a dosage range of 40 to 240 mg twice daily.

The 60 mg twice daily dose was determined to be the optimal dose as reduction in symptom severity was similar over the 40–240 mg dosage range, however, the 60 mg dose had a faster onset of action than the 40 mg dose. Significant symptom reduction was observed one hour following a single 60mg dose of fexofenadine hydrochloride. Onset of action was similar for doses of 60–240 mg.

In controlled clinical studies, fexofenadine hydrochloride 120 mg once daily was shown to relieve the symptoms of seasonal allergic rhinitis, significantly reducing total symptom scores (including scores for nasal congestion, sneezing, rhinorrhea, itchy nose, palate and/or throat, and itchy, watery, red eyes).

The incidence of drowsiness in controlled clinical seasonal allergic rhinitis trials was similar when comparing patients treated with fexofenadine hydrochloride (1.3%) and placebo (0.9%). There was no dose-related increase in drowsiness.

The effects of fexofenadine on the QT_c interval have been investigated in a variety of studies at doses up to 800 mg/day. There were no statistically significant differences in QT_c interval between fexofenadine hydrochloride and placebo patients. Similarly, there were no statistically significant differences from placebo of dose-related changes in other ECG parameters as a result of fexofenadine hydrochloride treatment.

Interaction studies involving erythromycin and ketoconazole demonstrated that, although the plasma AUC for fexofenadine increased approximately 2–3 fold, there were no significant effects on ECG, nor were there any effects on the incidence of adverse events. These changes in plasma levels were within the range of plasma levels achieved in adequate and well-controlled clinical trials.

The duration of the clinical studies presented for evaluation was limited to two weeks, however, studies on longer term use are ongoing.

5.2 Pharmacokinetic properties

Absorption

Fexofenadine hydrochloride is rapidly absorbed following oral administration. T_{max} occurred approximately 1-3 hours postdose. The mean C_{max} was approximately 142 ng/mL following the administration of a single 60 mg dose, approximately 289 ng/mL following a single 120 mg dose and approximately 494 ng/mL following a single 180 mg dose.

The absolute bioavailability following fexofenadine hydrochloride administration is calculated to be 33%.

Absorption of fexofenadine is not significantly altered by food.

Distribution

Fexofenadine is 60–75% bound to plasma proteins in healthy subjects.

Biotransformation

Fexofenadine undergoes negligible metabolism.

Elimination

Following a single 60 mg oral dose, 80% and 11.5% of total fexofenadine dose was excreted in the faeces and urine respectively. Following multiple dosing, fexofenadine has a mean terminal elimination half-life of 11-16 hours. The major route of elimination is believed to be biliary excretion while up to 10% of the ingested dose is excreted unchanged through the urine.

Linearity/non-linearity

The single and multiple dose pharmacokinetics of fexofenadine are linear between 20 mg and 120 mg doses. A dose of 240 mg twice daily produced slightly greater than proportional increase (8.8%) in steady state area under the curve.

The pharmacokinetics of fexofenadine in seasonal allergic rhinitis patients are similar to those in healthy subjects. One study indicated that females may be exposed to higher plasma levels than males, however, there was no indication of any difference in safety or efficacy. Elderly patients, patients with hepatic impairment and patients with cardiac disease exposed to fexofenadine by administration of terfenadine showed no statistically significant differences in pharmacokinetic parameters for fexofenadine compared to healthy individuals. Although peak plasma level and half-life were increased 68% and 15% respectively in elderly patients and 54% and 19% respectively in patients with renal disease regardless of disease severity, these levels are within the range of plasma levels shown to be well tolerated in adequate and well controlled safety and efficacy trials.

5.3 Preclinical safety data

The carcinogenic potential of fexofenadine was assessed using terfenadine studies with supporting pharmacokinetics studies showing fexofenadine exposure (via plasma AUC values). No evidence of carcinogenicity was observed in rats and mice given terfenadine.

Fexofenadine was found not to be mutagenic in various *in vitro* and *in vivo* mutagenicity tests.

6. Pharmaceutical Particulars

6.1 List of excipients

Xergic tablets (new formulation) contain powdered cellulose, mannitol, maize starch, croscarmellose sodium, colloidal silicon dioxide and magnesium stearate. The pink film coating contains hypromellose, titanium dioxide, macrogol, allura red AC lake (FD&C red #40) (E129) and iron oxide black (E172).

Xergic is gluten, lactose and sugar free.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at or below 25°C.

6.5 Nature and contents of container

PVC/PE/PVDC/Al blister pack.

Pack sizes of 10, 15, 30, 50, 56, 100 tablets.

Not all strengths or pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Not applicable

7. Medicines Schedule

Pharmacy only medicine

8. Sponsor Details

Mylan New Zealand Ltd
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AUCKLAND
Telephone 09-579-2792

9. Date of First Approval

06 August 2015

10. Date of Revision of the Text

26 October 2017	Revise to SmPC format. Updated section 4.5.