sanofi aventis
Because health matters

Submission to the Medicines Classification Committee for:

RECLASSIFICATION OF FEXOFENADINE

28 July 2009

sanofi-aventis australia pty ltd
12-24 Talavera Road,
Macquarie Park NSW 2113
and
sanofi-aventis new zealand limited
56 Cawley Street
Ellerslie, Auckland 1051

TABLE OF CONTENTS

EXECUTIVE SUMMARY

Fexofenadine is an orally active non-sedating histamine H1-receptor antagonist which effectively relieves the symptoms of Allergic Rhinitis (AR). Fexofenadine was first registered in New Zealand in January 1997 and it is currently registered in over 115 countries worldwide.

Fexofenadine (when used in oral preparations) was granted immediate Pharmacy Only status in New Zealand in November 1996. Similarly, in Australia this molecule became the first new chemical entity to be classified as a Schedule 3 substance, at the November 1996 NDPSC meeting. A subsequent application rescheduling fexofenadine (when used in oral preparations) to Schedule 2 was granted at the February 1999 NDPSC meeting.

Sanofi-aventis australia pty ltd limited seeks approval for a General Sales Medicine classification for fexofenadine. Specifically, this application seeks to facilitate the supply of a small (maximum 10 dosage units) oral presentation of fexofenadine, when used only for the short-term treatment (maximum 5 days of therapy) of Seasonal Allergic Rhinitis (SAR) in adults and children 12 years and over, with a maximum daily dose of 120 mg.

A summary of the arguments supporting this proposal is enclosed below:

- Allergic rhinitis (AR) is estimated to affect 18% of those aged 15-34 years and 10% of older adults aged 35-54 years and its prevalence over the last 10-15 years has almost doubled[1].
- Seasonal Allergic Rhinitis (SAR) is a self-limiting condition recognised as being appropriate for self-diagnosis. Currently, there are a large number of products available for patient self-selection for this condition.
- Fexofenadine is a non-sedating antihistamine which effectively relieves the symptoms of SAR. It has rapid onset and long duration of action, allowing for a convenient once a day administration.
- Broader access to fexofenadine (including after pharmacy closing hours) will allow for convenient access, during the times when symptoms are often worst, to an effective, long lasting and safe SAR treatment choice. Thus patients, particularly ‘experienced’ SAR sufferers who have indicated that availability of hayfever medications outside of normal pharmacy trading hours was useful,

will be able to manage their condition most effectively and reduce SAR's impact on their quality of life.

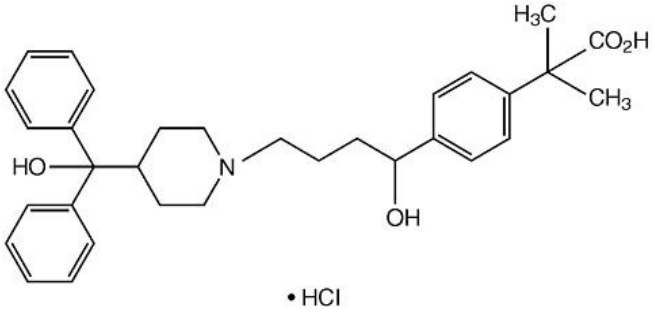
- Fexofenadine has minimal clinically-significant drug interactions and contraindications, and a long and established history of safe and effective use in New Zealand, Australia and over 115 other international markets.
- Fexofenadine is suitable for a wide range of patients including the elderly and patients with hepatic and/or renal insufficiency, without the need for dosage adjustment.
- Fexofenadine is highly selective for peripheral H_1-receptors and does not cross the blood-brain barrier. Therefore, it has a minimal incidence of sedation and does not impair performance or driving ability. There is minimal potential for abuse/misuse of fexofenadine and no reports of illicit diversion.
- In the event that a consumer was to misuse fexofenadine following misdiagnosis of the common cold, the most likely outcome is that the cold will simply resolve spontaneously in time, leaving the consumer with no negative sequalae.
- A maximum pack size of 10 dosage units (smaller than any presentation currently available in pharmacies) and maximum therapy duration of 5 consecutive days will help to facilitate only short-term use of fexofenadine as a General Sales Medicine. Additionally, appropriate pregnancy and breast-feeding warnings and a redirection to the Pharmacist should symptoms persist will be included on product labelling, as well as a Consumer Medicine Information (CMI) leaflet in the package to maximise the safe and effective use of fexofenadine.

In conclusion, sanofi-aventis contend that a General Sales Medicine classification for oral fexofenadine with appropriate indication, duration of treatment and dose restrictions for use, for the purpose of convenience and access to medicines offers a significant benefit to patients afflicted with SAR.

PART A

1. International Non-proprietary Name (or British Approved Name or US Adopted Name) of the medicine

Fexofenadine hydrochloride is an equimolar mixture of two enantiomers. Its chemical information is described below:

INN/BAN:	fexofenadine hydrochloride
Chemical name:	benzeneacetic acid, 4-[1-hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]butyl]-α,α-dimethyl-, hydrochloride.
Chemical Structure:	
Molecular formula:	$C_{32}H_{39}NO_4.HCl$
Molecular Weight:	538.12
CAS Registry Number:	153439-40-8

2. Proprietary name(s)

Telfast®

3. Name of company/organisation/individual requesting reclassification

sanofi-aventis australia pty ltd
12-24 Talavera Road,
Macquarie Park NSW 2113
AUSTRALIA
and
sanofi-aventis new zealand limited
56 Cawley Street
Ellerslie, Auckland 1051
NEW ZEALAND

4. Dose form(s) and strength(s) for which a change is sought

Product:	File ref:	Pack sizes:	Current Classification:
Telfast Capsule, 60mg	TT50-5726	4, 10	Pharmacy only
Telfast Film coated tablet, 120mg	TT50-5726/1	2, 5	Pharmacy only
Telfast Film coated tablet, 60mg	TT50-5726/1b	2, 10	Pharmacy only

5. Pack size and other qualifications

The current application seeks approval for a reclassification to a General Sale Medicine for a small (maximum 10 dosage units) oral presentation of fexofenadine, when used only for the short-term treatment (maximum 5 days of therapy) of Seasonal Allergic Rhinitis (SAR) in adults and children 12 years and over, with a maximum daily dose of 120 mg.

Accordingly, the only presentations of fexofenadine which will be suitable for sale as a General Sale Medicine are the 60 mg and 120 mg, in packs of 2 and 10 or 2 and 5 tablets, respectively. These proposed presentations are not currently available in New Zealand and are intentionally smaller than any presentation currently available in pharmacies. The proposed maximum of 5 days therapy will facilitate short-term use of fexofenadine. Similarly, the restriction on dose (maximum of 120 mg per day) and indication (only SAR) will also serve to selectively target patient use. The patient will be instructed (both in the packaging and package leaflet) to consult a pharmacist for further advice on the management of this condition should symptoms persist.

6. Indications for which change is sought

Seasonal Allergic Rhinitis (SAR).

7. Present classification of medicine

Pharmacy Only Medicine.

8. Classification sought

General Sale Medicine.

9. Classification status in other countries (especially Australia, UK, USA, Canada)

Fexofenadine for oral use is classified as a Pharmacy Medicine in Australia. An application seeking an exemption from scheduling is under consideration.

For commercial reasons, sanofi-aventis has not requested non-prescription status in either the UK or USA. However, most antihistamines, including first generation antihistamines (shown to cause significant sedation, drowsiness and impaired function similar to that resulting from high levels of alcohol in blood) are readily available without prescription in USA. Similarly, in the UK cetirizine and loratadine, with similar efficacy to fexofenadine but a higher reported incidence of sedation, have also been available without prescription since 1988 and are therefore, as in the USA, readily available for patient self-selection.

10. Extent of usage in NZ and elsewhere (e.g. sales volumes) and dates of original consent to distribute

Fexofenadine was first marketed on the 19 August 1996 in the USA and is currently marketed in more than 115 countries worldwide, including the USA, Canada, New Zealand and throughout Europe. In New Zealand, fexofenadine was first launched in June 1997 and in Australia in February 1997.

Sales volumes (Unit Sales) of fexofenadine products in New Zealand, by strength and year, for the past 5 years are presented below:

Source: IMS

Total	MAT Feb 2005	MAT Feb 2006	MAT Feb 2007	MAT Feb 2008	MAT Feb 2009
60mg	28,329	22,935	18,773	17,377	15,332
120mg	59,864	47,103	39,726	40,818	34,437
180mg	52,851	68,559	77,773	88,182	92,941

In New Zealand, fexofenadine is indicated for the relief of symptoms associated with SAR in children aged 6 to 11 years, and the relief of symptoms associated with AR (ie. seasonal and perennial allergic rhinitis) or chronic idiopathic urticaria in adults and children aged 12 years or older. The sales volumes presented above are not differentiated by indication and therefore include all fexofenadine containing products in the New Zealand market, sold for the treatment of SAR, PAR and urticaria, in both children and adults.

11. Labelling or draft labelling for the proposed new presentation(s)

The carton labelling for the proposed unclassified presentations will be essentially similar to that of the current Pharmacy Only Medicine product with the additional restrictions on indications and duration of therapy and additional warning statements as described in Section 12 below. A copy of the proposed labelling is included in Appendix 1 for your convenience.

Although not formally required in New Zealand, sanofi-aventis also propose the inclusion of a printed leaflet, to be provided in the form of a Consumer Medicine Information (CMI). Inclusion of a CMI as a pack insert is in accordance with the principles of the Quality Use of Medicines. The format of the proposed CMI has been based on that which is currently recommended by the Australian Usability Guidelines, which is also in accordance with the information described in the New Zealand Regulatory Guidelines for Medicines Volume 4: Consumer Medicine Information. The explicit intent for inclusion of the CMI is to direct patients to the appropriate Healthcare Professional to ensure that those patients requiring additional counselling are able to source it. A copy of the proposed CMI is included in Appendix 1 for your reference. The indications, dosage recommendations as well as the instruction to consult a pharmacist should symptoms persist will be clearly emphasized.

12. Proposed warning statements if applicable

The following warning statements or statements to the same effect will be included:

- Do not use in children under 12 years.
- Do not take more than the recommended dose.
- If you are breast-feeding or pregnant, or may become pregnant, check with your pharmacist or doctor before taking this medicine.
- If symptoms persist after 5 days, consult your pharmacist.
- 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.
- Read the enclosed leaflet for additional information.

Furthermore, unlike the current Pharmacy Only Medicine fexofenadine presentation, it is proposed that the small General Sale Medicine presentations of fexofenadine will include patient leaflets which also reinforce consultation with health professionals prior to use in pregnancy and breast-feeding.

13. Other products containing the same active ingredient(s) and which would be affected by the proposed change

A summary of all the products containing fexofenadine 60mg or 120mg registered in New Zealand is enclosed below.

Product	Sponsor
Fexofast 120 Tablet, 120mg (Pharmacy only)	Arrow Pharmaceuticals (NZ) Limited
Fexofenadine Film coated tablet, 120mg (Pharmacy only)	Douglas Pharmaceuticals Ltd
Fexofenadine Film coated tablet, 120mg, Affordable Healthcare (Pharmacy only)	Dr Reddy's New Zealand Limited
Fexofenadine Tablets - Rex Film coated tablet, 120mg (Pharmacy only)	REX Medical Ltd
Xergic Film coated tablet, 120mg (Pharmacy only)	Mylan New Zealand Limited
Xergic Film coated tablet, 60mg (Pharmacy only)	Mylan New Zealand Limited

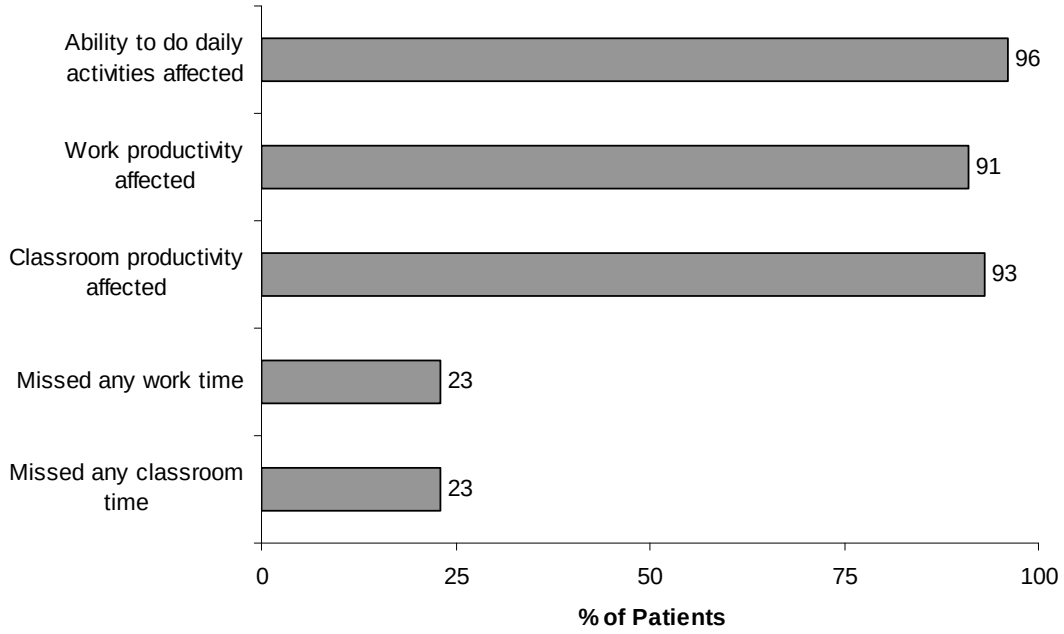
PART B

1. Benefits to both the consumer and to the public expected from the proposed change

Fexofenadine is an effective SAR treatment option, proven to improve the quality of life of SAR patients. It is rapidly absorbed and has an extended duration of action, making it suitable for a convenient once-daily administration. Fexofenadine has minimal clinically significant drug interactions (refer to Section B6) and contraindications (refer to section B7) other than hypersensitivity to the ingredients. Fexofenadine is also highly selective for peripheral H1-receptors and does not cross the blood-brain barrier. Therefore, the incidence of sedation is very low and there is no evidence of fexofenadine causing impairment of performance or driving ability.

Fexofenadine is also suitable for a wide range of patients including the elderly and patients with hepatic and/or renal insufficiency, without the need for dosage adjustments. 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 tolerated in short term dose ranging trials[2].

The quality of life of patients afflicted with SAR can be greatly diminished by their condition. Typically, SAR can lead to impaired performance of daily activities, cognitive function and classroom productivity, and reduced psychological wellbeing[1, 3, 4]. A study of the effect of fexofenadine on the quality of life and work, classroom, and daily activities of patients with SAR reported that close to 100% of patients felt that their ability to perform daily activities, work or classroom productivity was negatively affected by their SAR symptoms. In addition, approximately one-quarter of patients reported missing some work or school due to their symptoms. These results are presented graphically below and clearly show the human impact associated with SAR[5, 6]:



Convenient and timely access to effective and well-tolerated treatment for SAR would therefore be clearly advantageous, as it would provide optimal symptom control thus reducing the impact of SAR on wellbeing and performance.

An online Omnibus survey of Panel Pharmacists was conducted in Australia to investigate current trading hours and the management of SAR. Participating Panel Pharmacists voluntarily complete these Guild-approved surveys via an embedded link to the web following an e-mail notification to a random sample of the Panel. The Panel was developed by sending invitations to a random sample of practicing Pharmacists - which currently includes a reasonable representation of demographics such as location, sex, employees vs owners - from the total Australian population, with regular rotation of the Panel sample[7].

Of 150 pharmacists surveyed, just over 50% of these reported pharmacy opening hours of 9 am to 6 pm or 8 am to 6pm (7 days a week), while about 30% were said to have trading hours of 8 to 9 hours/day but less than 7 days a week. Only 4% of pharmacies were open 24 hours/7 days a week[7].

Another omnibus survey of 2,100 consumers over the age of 18 years on the topic of SAR was recently conducted in Australia over two rounds on 1-3 May and 15-17 May 2009. The survey was conducted using Computer-Assisted Telephone Interviews with telephone numbers randomly selected from the electronic White Pages. Interviewers were trained and briefed on the study and age, gender and regional

quotas that were to apply. Following completion of interviewing, the data was weighted by age, gender and region to reflect the latest ABS population estimates. The sample was distributed throughout Australia as follows: NSW/ACT 627; VIC/TAS 586; QLD 385; SA 250 and WA 252. The survey revealed that 29% of Australians suffered from hayfever during the spring 2008 and summer 2008-2009 hayfever season[8].

Of these Australians who suffered from hayfever last season, 72% treated their condition with medication, equating to more than 3.4 million Australian adults treating hayfever with medication each year. Of the hayfever patients who treated their condition with medication (437 out of the 2,100 respondents), the following responses were received regarding the timing and predictability of symptoms. Symptoms of SAR appear to be at their worst in the early morning (between 5:00 to 8:00 am) or evening (between 6:00 pm to 5:00 am) in 26% and 16% of hayfever patients who treated their condition. This is consistent with published data on the diurnal variation in AR symptomology with most troublesome symptoms reported to occur early in the morning or overnight in up to 75% of patients[8, 9, 10].

Regarding the onset of their symptoms, 56% of respondents in the Omnibus survey indicated that their symptoms come on unexpectedly, without warning and that they do not always keep hayfever medication with them for immediate relief. The survey also assessed patients' access to hayfever treatment and their preference for purchasing medication. Thirty three percent of patients revealed that they have not been able to purchase medication whilst suffering from SAR (on at least one occasion) because pharmacies were closed, and 81% of 'hayfever treaters' indicated that they would find it useful to be able to purchase hayfever medication outside of normal trading hours of pharmacy.[8]

The abovementioned surveys were conducted in order to support a rescheduling application currently under consideration in Australia. It would be cost prohibitive to repeat the same surveys for New Zealand. However, given the similar patient demographics, it is anticipated that the Australian results are equally relevant for New Zealand.

Given that the consumer Omnibus survey with SAR sufferers and published data indicate that symptoms are worse in the early morning or evening, that a majority of

sufferers report that their symptoms come on unexpectedly, and about one-third have been unable to purchase hayfever medication when symptoms arise outside of normal pharmacy opening hours, evidence is available to support reclassification of fexofenadine to enable access from grocery stores and other outlets.

Significantly, the consumer Omnibus survey revealed that more than three-quarters (81%) of experienced SAR sufferers were in support of making hayfever medication, such as fexofenadine, available outside of usual pharmacy trading hours[8].

The current application seeks approval for a General Sales Medicine classification for a small (maximum 10 dosage units) oral presentation of fexofenadine, when used only for the short-term treatment of SAR (maximum 5 days of therapy) in adults and children 12 years and over, with a maximum daily dose of 120 mg. The intent of this proposal is to facilitate the most convenient and timely access to 'emergency' fexofenadine for 'experienced' SAR sufferers, particularly early in the morning and over weekends when it is more likely that grocery stores and service stations, rather than pharmacies, are open. Of note, the proposed reclassification and limitation on dosage units (maximum of 10) would result in new, smaller 'emergency' pack sizes of fexofenadine in grocery, leaving the currently available larger pack sizes in pharmacy. Similarly, the restriction on dose (maximum of 120 mg per day) and indication (only SAR) will also serve to selectively target patient use.

Given the excellent safety profile of fexofenadine and the extent to which it has been safely used in a number of markets, including New Zealand and Australia, the conflicting temporal relationship between patients worst symptoms and usual pharmacy trading hours, sanofi-aventis consider that a General Sale Medicine classification of fexofenadine with appropriate limits on dose, pack size and indications will not impose any greater risk to the population than the current Pharmacy Only Medicine classification.

2. Ease of self-diagnosis or diagnosis by a pharmacist for the condition indicated

AR is the result of inflammation induced by a gamma globulin E (IgE)-mediated immune response to specific allergens. The immune response involves the release of inflammatory mediators and the activation and recruitment of cells to the nasal mucosa. Traditionally, AR has been subdivided into Perennial Allergic Rhinitis

(PAR) and Seasonal Allergic Rhinitis (SAR). PAR is mostly triggered by allergens such as indoor moulds, animal dander, dust mites and cockroaches and its symptoms are persistent and present year-round. The triggers for SAR can include a variety of outdoor allergens such as pollen grains from weeds, grasses, flowers and trees or moulds and symptoms usually appear during a specific season, such as spring and early summer. The signs and symptoms of SAR include rhinorrhea (runny nose), nasal obstruction, nasal itching, sneezing and watery eyes[4].

SAR can be easily self-diagnosed by the characteristic symptoms and is readily distinguishable from other forms of rhinitis due to its characteristic seasonal onset. Additionally, SAR is a self-limiting disorder which does not require special investigations and/or testing, and is unlikely to mask a more serious underlying disease.

There are currently a wide range of over-the-counter (OTC) treatments for SAR available in New Zealand. This condition has long been recognised as appropriate for self-diagnosis and most adult sufferers self-medicate for SAR. A 2002 survey of hayfever and allergy sufferers revealed that nearly two-thirds of respondents did not consult their doctor about their current SAR treatment[3].

Furthermore, in the event that a consumer was to misuse fexofenadine following misdiagnosis of the common cold, the most likely outcome is that the cold will simply resolve spontaneously in time, leaving the consumer with no negative sequalae.

3. Relevant comparative data for like compounds

Oral antihistamines have long been used as first-line therapy for allergic rhinitis. Whilst, older first-generation H1 antihistamines are effective at controlling rhinorrhea, sneezing and pruritus associated with SAR, as they cross the blood-brain barrier, they are associated with significant adverse effects, such as sedation which in turn can lead to impaired performance at home, work and school and driving impairment. Even when taken in the evening, these products may still cause significant residual daytime sedation, decreased alertness and performance impairment. The sedative side effects of first-generation antihistamines can also be greatly intensified by the concomitant consumption of alcohol[4, 11].

Consequently, the newer generation antihistamines are preferable therapeutic alternatives for the treatment of SAR.

When compared with other commonly used second generation antihistamines, fexofenadine offers obvious advantages. Unlike loratadine and cetirizine, which can produce central nervous system effects if used at dosages exceeding those recommended, fexofenadine at dosages up to 690 mg twice a day (nearly 8 times the maximum recommended daily dose of 180mg) has shown no differences in sedation relative to placebo. Therefore fexofenadine is a safe treatment option for people who need to drive or operate machinery[12].

Psychomotor tests confirm the safety of loratadine at the recommended dosage (10mg/day). However, significant impairment and sedation in objective performance tests has been shown in performance studies with higher, off-label doses of 20 and 40mg. Similarly, desloratadine at higher off-label doses has also been shown to cause somnolence[13]. In head-to-head studies, fexofenadine has also been shown to be more effective than loratadine at relieving the individual symptoms of nasal congestion and itchy, watery, red eyes and to have comparable efficacy to cetirizine[14].

Furthermore, in a study comparing the efficacy, safety and impact on quality of life in SAR patients of fexofenadine and loratadine (with placebo), fexofenadine was significantly better than loratadine in improving eye symptoms and nasal congestion and produced greater improvements in quality of life, to an extent considered to be clinically meaningful. When compared with placebo, loratadine had no statistically significant effects on quality of life[12, 15].

Although several clinical studies have shown that fexofenadine, as well as cetirizine, were significantly more efficacious than placebo in the treatment of SAR, fexofenadine has been found to be free of sedative effects even at higher than therapeutic doses. Cetirizine, even when given at therapeutic doses, can cause a slight to moderate increase in sedation, decreased psychomotor function and worsening cognitive function. Consequently, cetirizine is classified as mildly sedating which precludes its use in patients whose jobs require a high degree of alertness, concentration or psychomotor skills[13].

Furthermore, a recent study investigated fexofenadine effects on cognitive performance in aviators at both ground level and simulated altitude. The effects of fexofenadine were compared to both a placebo (passive control) and cetirizine (active control). During the entire test period, fexofenadine did not significantly affect

performance related to flight activities involving accuracy, speed, and attentiveness compared with placebo, at either atmospheric conditions or hypoxic conditions. Cetirizine however, increased Aeromedical Vigilance Test (AVT) errors significantly over the entire test period at 10,000ft and 15,000ft. The findings of this study further support the use of fexofenadine by personnel in occupations which demand constant attention, vigilance and alertness[16].

In 1999 an extensive review of literature (from 1965 to 1997) was published which investigated the sedative, psychomotor, and cognitive effects of available antihistamines. The studies reviewed were limited to placebo- and positive-controlled, performed with healthy volunteers, and most used standardized quantitative objective and subjective methods of measuring drug-induced effects on sedation, psychomotor performance, and cognition. The risk: benefit ratio for each antihistamine was calculated by dividing the number of discrete sedation tests in all studies that showed impairment with the number that showed no impairment. The results showed that fexofenadine had no sedative effects (risk: benefit ratio calculated to be 0.00) while cetirizine (risk: benefit ratio calculated to be 0.21) and loratadine (risk: benefit ratio 0.29) resulted in a relatively high level of cognitive and psychomotor impairment and sedation[17].

4. Local data or special considerations relating to NZ

Australia and New Zealand have among the highest prevalence of allergic disorders in the developed world. The Australasian Society of Clinical Immunology and Allergy (ASCIA) estimate for 2007 was that 4.1 million Australians (19.6% of the population) had at least one allergy; the highest prevalence of allergies in the working age population with 78% of 15 - 64 year olds suffering allergies and 7.2 million cases of allergy (ie. an average of 1.74 comorbid allergies per person). Allergic rhinitis (AR) is estimated to affect 18% of those aged 15-34 years and 10% of those 35-54 years, and its prevalence over the last 10-15 years has almost doubled[1]. Furthermore, the prevalence of AR also represents a significant economic burden, with the Australian Institute of Health and Welfare estimate for 1994 for respiratory disease (including AR) accounting for 8.0% of total healthcare system costs[3].

5. Toxicity and Safety of the Substance

The inherent safety of fexofenadine has been demonstrated extensively in both toxicological studies and human clinical trials. In addition, there is a long and established history of safe and effective use of fexofenadine in New Zealand and internationally, supported by extensive post-marketing surveillance data.

Therapeutic Dose

The recommended daily dose of fexofenadine for the treatment of SAR is 120 mg. This can be taken as either one 60 mg tablet twice daily, or a 120 mg tablet once daily. The antihistaminic activity of fexofenadine has been demonstrated at doses as low as 20 mg, whilst its safety has been demonstrated at doses up to 800 mg per day. At doses of 800 mg/day, which is greater than 4 times the recommended daily dose for urticaria, and 6 times the recommended daily dose for SAR, no clinically significant adverse events were reported from 40 patients treated for 6.5 days. Studies in healthy volunteers given fexofenadine hydrochloride 60 mg twice daily for 6 months or 240 mg once daily for 12 months showed no statistically significant change in safety or tolerability when compared to placebo. These data demonstrate the wide therapeutic index of fexofenadine hydrochloride, further reinforcing its exemplary safety and tolerability profile.

Cardiovascular Toxicity

Over the last 20 years, a number of cardiotoxic effects (torsades de pointes, prolongation of QTc interval, arrhythmia) have been reported in relation to certain second-generation antihistamines. These effects appear to be dose-dependent, a fact which is particularly important in relation to drugs metabolised by the P450 cytochrome, as concomitant administration of other drugs metabolised by the same enzyme may result in reduced rates of metabolism and consequently increased plasma concentrations.

Fexofenadine is not associated with ECG abnormalities and does not affect the action potential or ion channel currents (I_K, I_{Ca}, I_{Na}) in either guinea pig or neonatal rat myocytes. Fexofenadine was 583 times less potent than terfenadine in blocking a delayed rectifier potassium channel cloned from human heart. Additionally, doses of fexofenadine 10 times greater than the dose of terfenadine that produces prolongation of QTc intervals, did not prolong QTc intervals in anaesthetised rabbits and conscious dogs. The effects of fexofenadine on the QTc interval have also been investigated in

a variety of studies at doses up to 800 mg/day. There were no statistically significant differences in QTc interval between fexofenadine- and placebo-treated patients. Similarly, there were no statistically significant differences from placebo or dose-related changes in other ECG parameters as a result of fexofenadine treatment. Furthermore, no statistically significant change in QTc intervals was observed in long-term studies in healthy subjects given fexofenadine hydrochloride 60 mg twice daily for 6 months, or 240 mg once daily for 12 months, when compared to placebo[2, 18].

Chronic Toxicity and Overdosage

The long-term safety of fexofenadine has been shown in two placebo-controlled, double-blind, randomised and parallel-group design studies. Subjects received either placebo or 240 mg fexofenadine HCl once-daily for 12 months or placebo or 60 mg fexofenadine HCl twice daily for 6 months. As with short-term studies, there was no difference in the incidence of adverse events between fexofenadine and placebo. Fexofenadine was also not associated with significant changes in ECG parameters in either study[18]. Fexofenadine has been on the New Zealand market since June 1997 and is currently readily used as long term treatment of PAR.

Whilst there is no fully documented clinical experience with a fexofenadine overdose, single doses up to 800 mg and doses up to 690 mg twice daily for 1 month or 240 mg once daily for 1 year were studied in healthy subjects without the development of clinically significant adverse events as compared to placebo. In the case of an overdose, standard measures to remove any unabsorbed drug should be employed and symptomatic and supportive treatment is recommended[2].

Pregnancy and Lactation

Fexofenadine is classified as a Category B2 medicine in Australia. Reproductive toxicity of fexofenadine in animals was assessed through terfenadine exposure and 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. Decreased pup weight and survival occurred in rats when terfenadine was given at oral doses of 150 mg/kg/day and above throughout pregnancy and lactation. There are no studies in

pregnant women exposed to fexofenadine alone or through the administration of terfenadine[2].

Fexofenadine is not recommended for nursing women. There are no data on concentrations found in breast milk, however, when terfenadine was administered to nursing mothers, fexofenadine was found to cross into human breast milk[2].

Sanofi-aventis note that a Category A Pregnancy Classification is not a requirement for unclassified medicines. In addition, it is noted that several products are currently available as General Sale Medicines despite their Pregnancy Category and/or restriction on use during lactation eg. aspirin (Pregnancy Category C, not recommended during breast-feeding); ibuprofen (Pregnancy Category C); nicotine (Pregnancy Category D); ranitidine (Pregnancy Category B1). Similarly, several vitamin and mineral supplements which are readily available outside of pharmacist supervision are not recommended for use during pregnancy and/or lactation, but appear to be safely managed through adequate warnings included on labelling eg. high doses of vitamins A, D & E.

Given the available data on fexofenadine in pregnancy and breastfeeding, sanofi-aventis propose to include the following warning statement or a statement to the same effect on the proposed General Sales Medicine carton labelling (Appendix 1):

> 'If you are breast-feeding or pregnant, or may become pregnant, check with your pharmacist or doctor before taking this medicine'.

Furthermore, unlike the current Pharmacy Only Medicine fexofenadine presentation, it is proposed that the small unclassified presentations of fexofenadine will include patient leaflets which also reinforce consultation with health professionals prior to use in pregnancy and breast-feeding.

6. Interactions with other medicines

Fexofenadine has well characterised pharmacokinetic properties and undergoes minimal biotransformation in the body. Hepatic metabolism is of minimal importance in the elimination of fexofenadine, consequently, enzyme inhibition has little effect on its plasma concentrations.

Interaction studies in healthy volunteers with fexofenadine and erythromycin or ketoconazole demonstrated that although the plasma AUC for fexofenadine increased approximately 2 - 3 fold, there were no significant effects on mean or maximal QTc, nor were there any effects on the incidence of adverse events. Although these plasma levels were above those seen with the recommended dose, they were within the range of plasma levels achieved in controlled dose ranging clinical trials. The mechanism of these interactions has been evaluated in *in vitro*, *in situ*, and *in vivo* animal models. These studies indicate that ketoconazole or erythromycin co-administration enhances fexofenadine gastrointestinal absorption. This observed increase in the bioavailability of fexofenadine may be due to transport-related effects, such as p-glycoprotein. *In vivo* animal studies also suggest that in addition to enhancing absorption, ketoconazole decreases fexofenadine gastrointestinal secretion, while erythromycin may also decrease biliary excretion. Fexofenadine had no effect on the pharmacokinetics of erythromycin or ketoconazole[2, 19].

No interaction between fexofenadine and omeprazole has been observed. However, the administration of an antacid containing aluminium and magnesium hydroxide gel 15 minutes prior to fexofenadine hydrochloride causes a reduction in bioavailability, most likely due to binding in the gastrointestinal tract. Accordingly it is advised to leave 2 hours between administration of fexofenadine hydrochloride and aluminium and magnesium hydroxide containing antacids[2].

Fexofenadine is a substrate for P-glycoprotein, a membrane-bound transporter that inhibits absorption and promotes excretion. When consumed with grapefruit juice, the plasma concentration of fexofenadine can be decreased by 30 to 40%, as grapefruit has been shown to inhibit P-glycoprotein activity *in vitro*. Additionally, rifampicin can upregulate P-glycoprotein activity. Consequently, when taken with fexofenadine, peak plasma concentrations of fexofenadine are decreased. Nevertheless, it important to note that these effects have not been found to be clinically significant[4, 19].

7. Contraindications

Telfast is only contraindicated in patients with a known hypersensitivity to fexofenadine or any of its ingredients.[2]

8. Possible resistance

Not applicable.

9. Adverse events - nature, frequency etc.

Fexofenadine is generally well tolerated. The most common adverse events reported in controlled clinical trials were headache, fatigue, dizziness or drowsiness and nausea. The incidence of these effects was similar to that observed with placebo. No apparent dose trends were revealed in adverse events[2].

Post-Marketing Surveillance

The latest Periodic Safety Update Summary Bridging Report for fexofenadine and fexofenadine combinations is enclosed to this application in Appendix 2. This report integrates the information presented in the fexofenadine and fexofenadine/pseudoephedrine PSURs prepared by sanofi-aventis covering the 3-year period from 12 March 2005 to 11 March 2008. A calculation of the patient-years of therapy indicates that the number of patients exposed to fexofenadine (all formulations) worldwide for 1 year was 8,407,727 patients. From 12 March 2005 to 11 March 2008 (3 years) only 3,822 suspected ADR cases were received, further reinforcing the safety of this molecule. Of these, only 166 out of a total of 211 serious reports received for fexofenadine and fexofenadine/pseudoephedrine were assessed as unlisted. Based on the review of serious and non-serious adverse events during this reporting period, no new safety signal was detected for either fexofenadine or fexofenadine/pseudoephedrine and the benefit-risk profile of fexofenadine and fexofenadine/pseudoephedrine remains favourable.

10. Potential for abuse or misuse

Fexofenadine has been available in New Zealand since June 1997 and in Australia since February 1997. Moreover, although this product has been classified as an OTC for many years, during this time there has been no evidence of misuse, abuse or overuse of fexofenadine.

Fexofenadine does not cross the blood brain barrier, therefore in addition to minimising the incidence of drowsiness and sedation, there is minimal potential for abuse of this medicine. Additionally, there have been no reported cases of illicit drug diversion associated with this molecule.

Results from an online Omnibus survey in Australia completed by 150 pharmacists showed that more than one-third of patients (37%) seeking SAR medication do so as a result of self-diagnosis. Of these patients, two-thirds successfully self-diagnosed (67%) and only one third needed further assistance due to unsuccessful previous treatment (33%)[7]. It should be noted, however, that the main reason for patients requesting assistance with diagnosis was persistence of symptoms and having tried several treatment options that apparently failed, rather than inappropriate self-diagnosis. Although one-quarter of patients seek medication as a result of medical diagnosis, there is no reason to believe that these patients would be unable to successfully self-diagnose when faced with the same symptoms again.

The second most common reason in the Pharmacist Omnibus survey for patients requesting assistance with SAR was misdiagnosis with common cold[7]. Common cold symptoms can vary somewhat depending on the pathogen responsible. However, most of the viruses responsible for the common cold will produce some degree of nasal blockage, runny nose, cough and sore throat. Some of these symptoms can be effectively alleviated by antihistamines. Although some of the symptoms of SAR are non-specific (eg. nasal congestion and rhinorrhea), others such as nasal pruritus and ophthalmic symptoms, help differentiate it from common colds where they are absent. In addition, the onset of SAR is quite sudden which facilitates diagnosis as the common cold has usually a gradual onset and slow progression. Importantly, the common cold is also a self-limiting condition and any risk of misdiagnosis of either condition will be mitigated by the limitation of the dose and pack size for the General Sales Medicine presentation.

In the event that a consumer misdiagnoses the common cold as hayfever, and misuses fexofenadine as treatment of their symptoms, there is no risk of exacerbation of cold symptoms and the safety-profile would indicate that there is only a low risk of experiencing any adverse effects. Therefore, if fexofenadine does not alleviate nasal symptoms, and the consumer does not take any other remedial action, the most likely outcome is that the cold will simply resolve spontaneously in time, leaving the consumer with no negative sequalae.

Misuse of fexofenadine in the proposed presentations is also unlikely. The doses and pack sizes (smaller than any pack size available in pharmacies) and short term treatment (maximum 5 days of therapy) limit the use of the product. Additionally, the

presentations proposed to be unscheduled will contain a CMI leaflet with detailed information on the product to maximise the safe and effective use of fexofenadine. Moreover, patients will be instructed to consult a pharmacist should symptoms persist. Consequently, a General Sale Medicine classification for the proposed presentations is unlikely to pose any greater risk than the current Pharmacy Only classification.

CONCLUSION

SAR is a self-limiting condition long recognised as being appropriate for self-diagnosis and most New Zealanders now self-medicate for this condition. Beyond the immediate symptoms, SAR can also have a significant impact on patients' quality of life.

The therapeutic benefits of antihistamines for the treatment of SAR have been well established. However, not all second-generation antihistamines have established the same benefit: risk profile.

Fexofenadine is a highly specific H1-receptor antagonist with a wide therapeutic window and an excellent safety and tolerability profile. Fexofenadine provides fast-acting and highly effective sustained relief of the symptoms associated with SAR.

Fexofenadine does not cross the blood brain barrier, therefore in addition to minimising the incidence of drowsiness and sedation, there is minimal potential for abuse or illicit diversion of this medicine.

Fexofenadine has not been associated with the rare cardiotoxic effects of some other antihistamines, has minimal clinically significant drug interactions and no contra-indications. Fexofenadine is suitable for a wide range of patients including the elderly and patients with hepatic and or renal insufficiency, without the need for dosage adjustment. The safety of its long term use is also well established and fexofenadine is currently approved for the long term treatment of PAR.

In the event that a consumer was to misuse fexofenadine following misdiagnosis of the common cold, if fexofenadine did not alleviate their nasal symptoms, the most likely outcome is that the cold will simply resolve spontaneously in time, leaving the consumer with no negative sequalae.

Controlled patient access to fexofenadine outside of pharmacy (including after pharmacy closing hours) will allow for emergency access to an effective, long lasting and well-tolerated SAR treatment option. Accordingly, it is envisaged that experienced SAR sufferers can more effectively manage their condition and reduce SAR's impact on their quality of life.

The proposed limitation on dosage units (maximum of 10), smaller than any other fexofenadine presentation currently available in pharmacies, and the duration of therapy (maximum 5 days) will facilitate short-term emergency use of fexofenadine at times when sufferers are in need and experience their worst symptoms. Similarly the restriction on dose (maximum of 120 mg per day) and indication (only SAR) will also serve to selectively target patient use.

Importantly, the counselling role of pharmacists will not be altered by the proposed unclassified presentations. Pharmacies will continue to remain the primary supplier for fexofenadine and the management of this condition, particularly for treatment-naïve patients, long-term patients and children under 12 years. Similarly, for particularly resilient symptoms, the higher strength presentation will also only be available from pharmacies, and it is expected that patients would still refer to their pharmacist or doctor for further advice on the management of persistent symptoms.

In conclusion, sanofi-aventis contend that a General Sale Medicine classification for oral fexofenadine with appropriate indication, duration of treatment and dose restrictions, for the purpose of convenience and access to medicines offers a significant benefit to New Zealand patients afflicted with SAR without imposing any greater risk than its current classification.

APPENDICES

- APPENDIX 1 - PROPOSED LABELLING (CARTON LABEL AND CMI) FOR GENERAL SALES PRESENTATIONS

- APPENDIX 2 - SUMMARY BRIDGING REPORT - FEXOFENADINE AND COMBINATIONS; 12 MARCH 2005 - 11 MARCH 2008

APPENDIX 1

PROPOSED LABELLING (CARTON LABEL AND CMI)
FOR GENERAL SALES PRESENTATIONS

APPENDIX 2

SUMMARY BRIDGING REPORT - FEXOFENADINE AND COMBINATIONS
12 MARCH 2005 - 11 MARCH 2008

REFERENCES

[1] Access Economics Pty Limited for the Australasian Society of Clinical Immunology and Allergy (ASCIA). The economic impact of allergic disease in Australia: not to be sneezed at. 1-111, 2007

[2] Telfast Data Sheet 06 August 2007

[3] Walls RS, Heddle RJ, Tang MLK *et al***.** Optimising the management of allergic rhinitis: an Australian perspective. MJA 182: 28–33, 2005

[4] Lehman JM, Blaiss MS. Selecting the Optimal Oral Antihistamine for Patients with Allergic Rhinitis. Drugs 66 (18): 2309-2319, 2006

[5] Tanner LA, Reilly M, Meltzer EO, et al. Effect of fexofenadine on quality of life and work, classroom, and daily activity impairment in patients with seasonal allergic rhinitis. Am J Man Care 5(suppl):S235–S247, 1999

[6] Thompson AK, Juniper E, Meltzer EO. Quality of life in patients with allergic rhinitis. Ann Allergy Asthma Immunol. 85(5):338-47, 2000

[7] CSD Primary Market Research. Allergic Rhinitis, Pharmacist Online Omnibus Research, September 2008

[8] Galaxy Research. Accessibility of medication to treat seasonal hayfever in Australia, Consumer Computer-Assissted Telephone Interview Omnibus Research, May 2009

[9] Smolensky MH, Reinberg A, Labrecque G. Twenty-hour hour pattern in symptom intensity of viral and allergic rhinitis: Treatment implications. J Allergy Immunol 95: 1084-96, 1995

[10] Smolensky MH, Lemmer B, Reinberg A.. Chronobiology and chronotherapy of allergic rhinitis and bronchial asthma. Adv Drug Deliv Rev 59: 852-82, 2007

[11] Morgan MM, Khan DA, Nathan RA. Treatment for allergic rhinitis and chronic idiopathic urticaria: focus on oral antihistamines. Ann Pharmacother 9(12):2056-64, 2005

[12] Simpson K, Jarvis B. Fexofenadine. A Review of its Use in the Management of Seasonal Allergic Rhinitis and Chronic Idiopathic Urticaria. Drugs 59 (2): 301-321, 2000

[13] Golightly LK, Greos LS. Second-Generation Antihistamines. Actions and Efficacy in the Management of Allergic Disorders. Drugs 65 (3): 341-384, 2005

[14] Meeves SG, Appajosyula S. Efficacy and safety profile of fexofenadine HCl: a unique therapeutic option in H1-receptor antagonist treatment. J Allergy Clin Immunol. Oct; 112(4 Suppl):S69-77, 2003

[15] Van Cauwenberge P, Juniper EF. Comparison of the efficacy, safety and quality of life provided by fexofenadine hydrochloride 120 mg, loratadine 10 mg and placebo administered once daily for the treatment of seasonal allergic rhinitis. Clin Exp Allergy. 30(6):891-9, 2000

[16] Vacchiano C, Moore J, Rice GM, Crawley G. Fexofenadine effects on cognitive performance in aviators at ground level and simulated altitude. Aviat Space Environ Med. 79(8):754-60, 2008

[17] Hindmarch I, Shamsi Z. Antihistamines: models to assess the sedative properties, assessment of sedation, safety and other side effects. Clin Exp Allergy 29 (suppl 3):133-142, 1999

[18] Mason J, Reynolds R, Rao N. Fexofenadine.The systemic safety of fexofenadine HCl. Clin Exp Allergy 29 (supp 3): 163-170, 1999

[19] Pharmaceutical Press. Stockley's Drug Interactions 7th Ed 39, 420, 426, 428-430, 433, 863