sanofi-aventis australia pty ltd
12-24, Talavera Road
Macquarie Park NSW 2113

FEXOFENADINE HCL 60MG, 120MG, 180MG RECLASSIFICATION NEW ZEALAND

RECLASIFICATION APPLICATION

Fexofenadine Change to the 'Exemption from'
Reclassification Conditions from 'Pharmacy Only' to 'General Sale' Classification

29 July 2020

29/07/20

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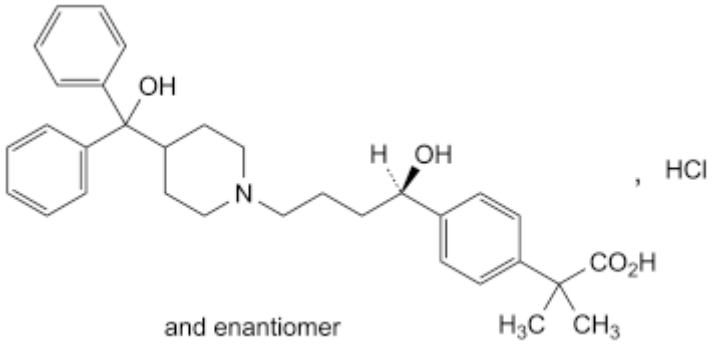
PART A

1 INTERNATIONAL NON-PROPRIETARY 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:	2-[4-[(1RS)-1-Hydroxy-4-[4-(hydroxydiphenylmethyl)piperidin-1-yl]butyl]phenyl]-2-methylpropanoic acid hydrochloride.

Chemical Structure:



Molecular formula: C32H40ClNO4

Molecular Weight:	538.1
CAS Registry Number:	153439-40-8

2 PROPRIETARY NAME(S).

Telfast ®

3 NAME OF THE COMPANY REQUESTING A RECLASSIFICATION.

sanofi-aventis Australia pty ltd

12-24 Talavera road

Macquarie Park NSW 2113
Australia
and
sanofi-aventis new zealand limited
PO Box 1285156 Penrose
Level 8, 56 Cawley Street
Ellerslie, Auckland 1051
NEW ZEALAND

4 DOSE FORM(S) AND STRENGTH(S) FOR WHICH A CHANGE IS SOUGHT.

Table 1 - Products for which the change is sought

Product:	File ref:	Pack sizes:	Current Classification:
Telfast Film coated tablet, 120mg	TT50-5726/1	10	Pharmacy only
Telfast Film coated tablet, 60mg	TT50-5726/1b	20	Pharmacy only
Telfast Film coated tablet, 180mg	TT50-5726/1a	5	Pharmacy Only

5 PACK SIZE AND OTHER QUALIFICATIONS.

Sanofi-aventis pty ltd requests two amendments of the reclassification conditions to General Sale Medicine.

Our first request is in relation to increasing the 60mg and 120mg fexofenadine pack sizes so that it is 'for the treatment of Seasonal Allergic Rhinitis (SAR), when used only in adults and children 12 years and over with a maximum daily dose of 120mg when sold in manufacturers original pack containing 20 dosage units or less and not more than 10 days' supply.'

Our second request is to amend the classification of fexofenadine to include the fexofenadine 180mg smaller pack size so that it is 'General Sale' when 'for the treatment of seasonal allergic rhinitis in adults and children 12 years of age and over…. when in tablets containing 180mg or less of fexofenadine hydrochloride with a maximum daily dose of 180mg when sold in the manufacturer's original pack containing 5 dosage units or less and not more than 5 days' supply.'

Currently fexofenadine is pharmacy only when it is administered orally except for the treatment of seasonal allergic rhinitis in adults and children 12 years and over when in capsules containing 60 milligrams or less of fexofenadine hydrochloride or in tablets containing 120mg or less of fexofenadine hydrochloride with a maximum daily dose of 120 milligrams when sold in the manufacturers original pack containing 10 dosage units or less and not more than 5 days' supply.

The proposed 60mg and 120 mg pack size change will support an increase in pack size of the general sale fexofenadine provided that there is no more than 10 days' supply in the pack. This proposed change aligns with a recent scheduling submission made in March 2016 for fexofenadine intended for the same indication in Australia and based on the Scheduling delegates' final decision which was approved in September 2016 and final decision published on the 27th of October 2016 confirming that the scheduling advice is appropriate (1), (2) which means that from the 1st of February 2017 fexofenadine was allowed to be sold in the grocery channels provided it met the criteria mentioned in the table below.

The proposed fexofenadine 180mg small pack size aligns with a recent interim scheduling decision made on the 10th of June 2020 for fexofenadine intended for the same SAR indication in Australia confirming that fexofenadine 180mg can be sold as General Sale with a 1 October 2020 date of effect of the proposed amendment as per the criteria mentioned in Table 2 below (3) (https://www.tga.gov.au/sites/default/files/notice-interim-decisions-proposed-amendments-poisons-standard-acmsaccsjoint-acms-accs-meetings-march-2020.pdf

Table 2 - Australian Scheduling wording

Australia Scheduling wording
Schedule 2*: FEXOFENADINE in preparations for oral use except in divided preparations for the treatment of seasonal allergic rhinitis in adults and children 12 years of age and over when: in a primary pack containing 20 dosage units or less and not more than 10 days' supply; and labelled with a recommended daily dose not exceeding 120 mg of fexofenadine. b) for the treatment of seasonal allergic rhinitis in adults and children 12 years of age and over when: in a primary pack containing 5 dosage units or less and not more than 5 days' supply; and labelled with a recommended daily dose not exceeding 180 mg of fexofenadine or Schedule 4*: FEXOFENADINE except when included in Schedule 2; or in divided preparations for the treatment for seasonal allergic rhinitis in adults and children 12 years of age and over when: in a primary pack containing 20 dosage units or less and not more than 10 days' supply; and labelled with a recommended daily dose not exceeding 120 mg of fexofenadine. for the treatment of seasonal allergic rhinitis in adults and children 12 years of age and over when: in a primary pack containing 5 dosage units or less and not more than 5 days' supply; and labelled with a recommended daily dose not exceeding 180 mg of fexofenadine. d) for the treatment of seasonal allergic rhinitis and children from 6 years of age when: in a primary pack containing 20 dosage units or less and not more than 10 days' supply; and labelled with a recommended daily dose not exceeding 60 mg of fexofenadine.

*In Australia S2 is considered Pharmacy Medicine (sold in pharmacy-only) whilst S4 is a Prescription medicine and kept behind the counter, requiring a script.

The proposed change in the fexofenadine 60mg and 120mg pack sizes also aligns with a recent scheduling submission made for loratadine intended for use for the same indication, for which an invitation to comment was published on the TGA website in November 2015. As there were no objections the delegate has approved the rescheduling of loratadine based on the interim decision (4).

In addition, as per the New Zealand Gazettal Notice from the 18th of August 2016 which is based on the 55th meeting of the Medicines Classification Committee held on the 3rd of May 2016 Loratadine has also been approved for General Sale use, when in divided solid dosage forms for oral use containing 10 milligrams or less per dose form for the treatment of seasonal allergic rhinitis when sold in the manufacturer's original pack containing not more than ten days' supply. (5)

6 INDICATIONS FOR WHICH CHANGE IS SOUGHT.

Seasonal Allergic Rhinitis (SAR) indication is sought for both proposed reclassifications.

7 PRESENT CLASSIFICATION OF THE MEDICINE.

Table 3 - Present Classification of Fexofenadine

Classification	Conditions
Prescription	except for oral use
Pharmacy Only*	for oral use except for the treatment of seasonal allergic rhinitis in adults and children 12 years of age and over when in capsules containing 60 milligrams or less of fexofenadine hydrochloride or in tablets containing 120 milligrams or less of fexofenadine hydrochloride with a maximum daily dose of 120 milligrams when sold in the manufacturer's original pack containing 10 dosage units or less and not more than 5 days' supply
General Sale	for the treatment of seasonal allergic rhinitis in adults and children 12 years of age and over when in capsules containing 60 milligrams or less of fexofenadine hydrochloride or in tablets containing 120 milligrams or less of fexofenadine hydrochloride with a maximum daily dose of 120 milligrams when sold in the manufacturer's original pack containing 10 dosage units or less and not more than 5 days' supply

*Currently the two proposed reclassifications are classified as Pharmacy Only Medicine.

Also note that the applicant currently distributes unscheduled fexofenadine under the brand name Telfast as 60 mg and 120 mg tablets. This application does not change the proposed dose Telfast tablets and only relates to extending the pack size of the fexofenadine hydrochloride 60mg and 120mg dosage units and to include the fexofenadine hydrochloride 180mg strength within the grocery range.

8 CLASSIFICATION SOUGHT.

General Sale Medicine.

To reflect the proposed increase in pack size for fexofenadine hydrochloride 60mg and 120mg and the proposed fexofenadine hydrochloride 180mg small pack size we provide in Table 4 below the current and proposed classification amendment:

Table 4 - Current and Proposed Amendment for Fexofenadine

Current Classification	Proposed Classification
Pharmacy Only for oral use except for the treatment of seasonal allergic rhinitis in adults and children 12 years of age and over when in capsules containing 60 milligrams or less of fexofenadine hydrochloride or in tablets containing 120 milligrams or less of fexofenadine hydrochloride with a maximum daily dose of 120 milligrams when sold in the manufacturer's original pack containing 10 dosage units or less and not more than 5 days' supply	Pharmacy Only for oral use except for the treatment of seasonal allergic rhinitis in adults and children 12 years of age and over when in capsules containing 60 milligrams or less of fexofenadine hydrochloride or in tablets containing 120 milligrams or less of fexofenadine hydrochloride with a maximum daily dose of 120 milligrams when sold in the manufacturer's original pack containing 20~~10~~ dosage units or less and not more than 10 ~~5~~ days' supply or in tablets containing 180mg or less of fexofenadine hydrochloride with a maximum daily dose of 180mg when sold in the manufacturer's original pack containing 5 dosage units or less and not more than 5 days' supply.'
General sale for the treatment of seasonal allergic rhinitis in adults and children 12 years of age and over when in capsules containing 60 milligrams or less of fexofenadine hydrochloride or in tablets containing 120 milligrams or less of fexofenadine hydrochloride with a maximum daily dose of 120 milligrams when sold in the manufacturer's original pack containing 10 dosage units or less and not more than 5 days' supply	General sale for the treatment of seasonal allergic rhinitis in adults and children 12 years of age and over when in capsules containing 60 milligrams or less of fexofenadine hydrochloride or in tablets containing 120 milligrams or less of fexofenadine hydrochloride with a maximum daily dose of 120 milligrams when sold in the manufacturer's original pack containing 20 ~~10~~ dosage units or less and not more than 10 ~~5~~ days' supply or in tablets containing 180mg or less of fexofenadine hydrochloride with a maximum daily dose of 180mg when sold in the manufacturer's original pack containing 5 dosage units or less and not more than 5 days' supply.

9 CLASSIFICATION STATUS IN OTHER COUNTRIES (ESPECIALLY AUSTRALIA, UK, USA, CANADA).

Country	Classification
USA	General Sale for adults and children 12 years and over indicated for SAR/PAR - containing 30 dosage units each 180 mg fexofenadine and not more than 30 days' supply; and labelled with a recommended daily dose not exceeding 180mg of fexofenadine. -containing 24 dosage units each 60 mg fexofenadine and not more than 24 days' supply; and labelled with a recommended daily dose not exceeding 120 mg of fexofenadine.
Australia	General Sale for adults and children 12 years and over indicated for SAR - containing 20 dosage units or less and not more than 10 days' supply; and labelled with a recommended daily dose not exceeding 120mg of fexofenadine. -containing 5 dosage units or less and not more than 5 days' supply; and labelled with a recommended daily dose not exceeding 180 mg of fexofenadine or Pharmacy Medicine (S2) for oral use unless it meets above criteria Prescription medicine unless it meets S2- Pharmacy medicine criteria

With a well-defined risk profile, fexofenadine has been made available through grocery channels in many markets including Australia, USA and NZ for a number of years. In other markets including the USA, both larger pack sizes and higher strengths such as 60mg – 24s and 180mg in 24s and 30s of fexofenadine are available through grocery channels with no evidence of any impact on the overall benefit/risk profile. In New Zealand fexofenadine became general sale

medicine as per the recommendation made in the MCC 42nd meeting (6) provided it meets criteria outlined in Table 4 Section 8 in the current column.

In Australia fexofenadine has been successfully reclassified to include the larger pack sizes for the 60mg and 120mg fexofenadine hydrochloride dosage units with an implementation date of the 1st of February 2017 (2)(3) under the following reclassification conditions:

Fexofenadine is Schedule 4 (Prescription medicine) except:
When included in Schedule 2; or
In divided preparations for oral use for the treatment of seasonal allergic rhinitis in adults and children 12 years of age and over when:
In a primary pack containing 20 dosage units or less and not more than 10 days' supply; and
Labelled with a recommended daily dose not exceeding 120mg of fexofenadine.

Fexofenadine is Schedule 2 in preparations for oral use except:
In divided preparations for the treatment of seasonal allergic rhinitis in adults and children 12 years of age and over when:
In a primary pack containing 20 dosage units or less and not more than 10 days' supply; and
Labelled with a recommended daily dose not exceeding 120mg of fexofenadine.

The reclassification of fexofenadine to General Sale in Australia provided it meets the above mentioned criteria supports the proposal to revise the current classification conditions in New Zealand to allow consumers to benefit from the flexibility and convenience of access and to be able to access larger packs, noting the proposed pack sizes still remains small.

The proposed fexofenadine 180mg change aligns the Australian recent interim scheduling decision made on the 10th of June 2020 (3) for fexofenadine intended for the same SAR indication in Australia confirming that fexofenadine 180mg can be sold as General Sale with a 1 October 2020 date of effect of the proposed amendment as per the criteria mentioned below:

Schedule 2*:
FEXOFENADINE in preparations for oral use except in divided preparations
for the treatment of seasonal allergic rhinitis in adults and children 12 years of age and over when:
in a primary pack containing 20 dosage units or less and not more than 10 days' supply; and
labelled with a recommended daily dose not exceeding 120 mg of fexofenadine.
b) for the treatment of seasonal allergic rhinitis in adults and children 12 years of age and over when:
in a primary pack containing 5 dosage units or less and not more than 5 days' supply; and
labelled with a recommended daily dose not exceeding 180 mg of fexofenadine or
Schedule 4**:
FEXOFENADINE except
when included in Schedule 2; or

in divided preparations for the treatment for seasonal allergic rhinitis in adults and children 12 years of age and over when:
in a primary pack containing 20 dosage units or less and not more than 10 days' supply; and labelled with a recommended daily dose not exceeding 120 mg of fexofenadine.
for the treatment of seasonal allergic rhinitis in adults and children 12 years of age and over when:
in a primary pack containing 5 dosage units or less and not more than 5 days' supply; and labelled with a recommended daily dose not exceeding 180 mg of fexofenadine.
d) for the treatment of seasonal allergic rhinitis and children from 6 years of age when:
in a primary pack containing 20 dosage units or less and not more than 10 days' supply; and labelled with a recommended daily dose not exceeding 60 mg of fexofenadine.

*Schedule 2 in Australia is equivalent to 'Pharmacy-Only' classification in New Zealand.
** Schedule 4 in Australia is equivalent to 'Prescription' classification in New Zealand

10 EXTENT OF USAGE IN NEW ZEALAND AND ELSEWHERE (EG, 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 120 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 and Australia, by strength, pack size and year, for the past 5 years are presented below in Table 5 and Table 6

Table 5 - Sales volumes (Unit Sales) of fexofenadine products in New Zealand, by strength and year, past 5 years

Product	2015	2016	2017	2018	2019
[redacted]					

Product	2015	2016	2017	2018	2019
[redacted]					

Table 6 - IRI Scan Data in NZ for past two years*

Product:	National Combined Units Year 2018	National Combined Units Year 2019
[redacted]		

*Note the above does not capture some of the other channels we sell our products such as Chemist Warehouse where there is strong demand for Telfast products.

In New Zealand, fexofenadine is indicated for the relief of symptoms associated with SAR in children aged 12 years and over, and also for the relief of symptoms associated with AR (ie. seasonal and perennial allergic rhinitis) or 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 tablet format in the New Zealand market, sold for the treatment of SAR, PAR and urticaria, in adults.

Table 7 - Sales volumes (Unit Sales) of fexofenadine products in Australia, by strength and year, past 5 years

Channel	Pack/SKU	Unit Sales June 2018	Unit Sales June 2019	Unit Sales May 2020
[redacted]				

Table 8 - Medsafe approved fexofenadine hydrochloride 60mg, 120mg and 180mg registrations including Telfast and generics

Product	Sponsor	Status
APOHEALTH Fexofenadine (see APOHEALTH Fexofenadine 180 Hayfever & Allergy Relief Film coated tablet, 180 mg (Pharmacy only))	Apotex NZ Ltd	Not available
APOHEALTH Fexofenadine 120 Hayfever & Allergy Relief Film coated tablet, 120 mg (General sale)	Apotex NZ Ltd	Not available
APOHEALTH Fexofenadine 120 Hayfever & Allergy Relief Film coated tablet, 120 mg (Pharmacy only)	Apotex NZ Ltd	Not available
APOHEALTH Fexofenadine 180 Hayfever & Allergy Relief Film coated tablet, 180 mg (Pharmacy only)	Apotex NZ Ltd	Not available
Fexaclear Film coated tablet, 120 mg (Pharmacy only)	Dr Reddy's New Zealand Limited	Consent given
Fexaclear Film coated tablet, 120 mg (General sale)	Dr Reddy's New Zealand Limited	Consent given
Fexaclear Film coated tablet, 180 mg (Pharmacy only)	Dr Reddy's New Zealand Limited	Consent given
Fexofast 120 Tablet, 120 mg (Pharmacy only)	Teva Pharma (New Zealand) Limited	Consent given
Fexofast 180 Tablet, 180 mg (Pharmacy only)	Teva Pharma (New Zealand) Limited	Consent given
Fexofenadine Film coated tablet, 120 mg (Pharmacy only)	Douglas Pharmaceuticals Limited	Not available
Fexofenadine Film coated tablet, 120 mg, Rex (Pharmacy only)	REX Medical Ltd	Consent given
Fexofenadine Film coated tablet, 180 mg (Pharmacy only)	Douglas Pharmaceuticals Limited	Not available
Fexofenadine Film coated tablet, 180 mg, Rex (Pharmacy only)	REX Medical Ltd	Consent given
Fexofenadine Hayfever & Allergy Relief Film coated tablet, 180 mg, Pharmacy Health (Pharmacy only)	PSM Healthcare Ltd trading as API Consumer Brands	Consent given

Product	Sponsor	Status
Hayfexo Film coated tablet, 120 mg (Pharmacy only)	Dr Reddy's New Zealand Limited	Consent given
Hayfexo Film coated tablet, 180 mg (Pharmacy only)	Dr Reddy's New Zealand Limited	Consent given
Medreich Fexofenadine Film coated tablet, 120 mg (General sale)	Medreich New Zealand Limited	Consent given
Medreich Fexofenadine Film coated tablet, 120 mg (Pharmacy only)	Medreich New Zealand Limited	Consent given
Medreich Fexofenadine Film coated tablet, 180 mg (Pharmacy only)	Medreich New Zealand Limited	Consent given
Medreich Fexofenadine Film coated tablet, 60 mg (General sale)	Medreich New Zealand Limited	Consent given
Medreich Fexofenadine Film coated tablet, 60 mg (Pharmacy only)	Medreich New Zealand Limited	Consent given
Telfast Film coated tablet, 120 mg (Pharmacy only)	sanofi-aventis new zealand limited	Consent given
Telfast Film coated tablet, 180 mg (Pharmacy only)	sanofi-aventis new zealand limited	Consent given
Telfast Film coated tablet, 60 mg (Pharmacy only)	sanofi-aventis new zealand limited	Consent given
Telfast Tablet, 120 mg (General sale)	sanofi-aventis new zealand limited	Consent given
Telfast Tablet, 60 mg (General sale)	sanofi-aventis new zealand limited	Consent given
Xergic Film coated tablet, 120 mg, New Formulation (Pharmacy only)	Mylan New Zealand Ltd	Not available
Xergic Film coated tablet, 180 mg, New Formulation (Pharmacy only)	Mylan New Zealand Ltd	Not available
Xergic 180 Film coated tablet, 180 mg, . (Pharmacy only)	Mylan New Zealand Ltd	Not available

11 LOCAL DATA OR SPECIAL CONSIDERATIONS RELATING TO NEW ZEALAND

There is growing evidence of a rise in the prevalence of allergic diseases, including rhinitis, over recent decades. It is estimated that approximately 20 per cent of the New Zealand population suffers from allergic rhinitis.(7) Hence, increasing the availability of the larger pack sizes of the 60mg and 120mg and the small pack size of the 180mg dosage units as "General Sale" will really benefit those SAR sufferers in New Zealand.

12 LABELLING OR DRAFT LABELLING FOR THE PROPOSED 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 restrictions on duration of therapy and additional warning statements as can be seen from the examples of the artwork below and as described in Section 13 below. Note that these are only mock ups and we will ensure compliance with the Medsafe Labelling Database.

Proposed front of pack for fexofenadine 60mg:

Proposed back of pack for fexofenadine 60mg:

Medicine Information

ACTIVE INGREDIENT	PURPOSE
fexofenadine hydrochloride 60mg	antihistamine

USES

Relief of the symptoms of hayfever allergies:
- Sneezing
- Itchy & runny nose
- Itchy throat
- Itchy & watery eyes

WARNINGS

Do not use:
- If you are pregnant or breastfeeding unless advised by a doctor or pharmacist.
- In children under 12 years.
- More than recommended dose.
- For more than 10 days at a time.
- With other antihistamines.
- If blister seal is broken.

Keep out of reach of children.
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.

DIRECTIONS FOR USE

Who can use this product:
Adults and children over 12 years.
How many: 1 tablet. **How often:** Twice daily as required.

Proposed front of pack for fexofenadine 120mg:

Proposed back of pack for fexofenadine 120mg:

Medicine Information

ACTIVE INGREDIENT	PURPOSE
fexofenadine hydrochloride 120mg	antihistamine

USES

Relief of the symptoms of hayfever allergies:
- Sneezing
- Itchy & runny nose
- Itchy throat
- Itchy & watery eyes

WARNINGS

Do not use:
- If you are pregnant or breastfeeding unless advised by a doctor or pharmacist.
- In children under 12 years.
- More than recommended dose.
- For more than 10 days at a time.
- With other antihistamines.
- If blister seal is broken.

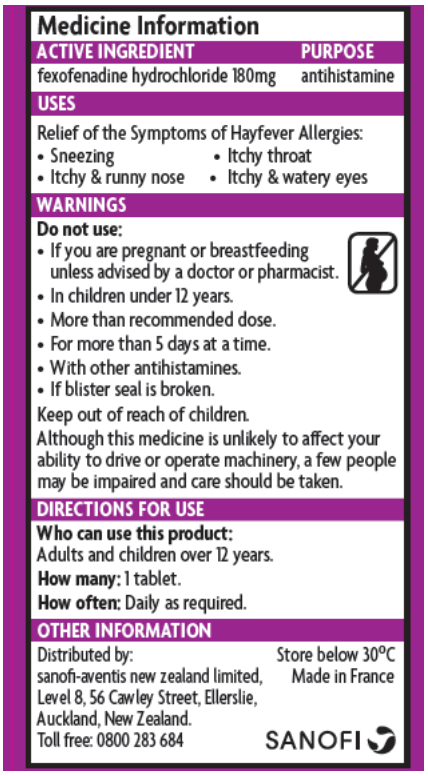
Keep out of reach of children.
Although this medicine is unlikely to affect your ability to drive or operate machinery, a few people may be impaired and care should be taken.

DIRECTIONS FOR USE

Who can use this product:
Adults and children over 12 years.
How many: 1 tablet. **How often:** Daily as required.

Proposed front of pack for fexofenadine 180mg:

Proposed back of pack for fexofenadine 180mg:



Medicine Information

ACTIVE INGREDIENT	PURPOSE
fexofenadine hydrochloride 180mg	antihistamine

USES

Relief of the Symptoms of Hayfever Allergies:
- Sneezing
- Itchy throat
- Itchy & runny nose
- Itchy & watery eyes

WARNINGS

Do not use:
- If you are pregnant or breastfeeding unless advised by a doctor or pharmacist.
- In children under 12 years.
- More than recommended dose.
- For more than 5 days at a time.
- With other antihistamines.
- If blister seal is broken.

Keep out of reach of children.

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.

DIRECTIONS FOR USE

Who can use this product:
Adults and children over 12 years.

How many: 1 tablet.

How often: Daily as required.

OTHER INFORMATION

Distributed by:
sanofi-aventis new zealand limited,
Level 8, 56 Cawley Street, Ellerslie,
Auckland, New Zealand.
Toll free: 0800 283 684

Store below 30°C
Made in France

SANOFI

Please refer to Appendix 1 for the current and draft labelling of the proposed presentations.

13 PROPOSED WARNING STATEMENTS IF APPLICABLE.

Fexofenadine 60mg and 120mg larger pack size:

The existing labelling information and precautionary statements for fexofenadine 60mg and 120mg general sale pack sizes have been found to be suitable in mitigating any risks and include the following information as per the New Zealand Label Statements Database with some minor adjustments in line with the two reclassification proposals:

Table 9 - Warning statements to be included on the back of pack of the carton label

Current Warnings:	Additional/revised warning statements (in red):
Do not use: -If you are pregnant or breastfeeding unless advised by a doctor or pharmacist -In children under 12 years -If blister seal is broken 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.	Do not use: -If you are pregnant or breastfeeding unless advised by a doctor or pharmacist - In children under 12 years -more than the recommended dose -for more than 10 days at a time. If symptoms persist after 10 days consult your doctor or pharmacist.(*applicable to the larger 60mg and 120mg pack sizes) -for more than 5 days at a time. If symptoms persist after 5 days consult your doctor or pharmacist.* (applicable to the small 180mg pack size) -with other antihistamines -If blister seal is broken Keep out of reach of children 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.

*Statement not added to the mock ups but will be added at time of updating submission.

The statement 'Do not use for more than 10 days. If symptoms persist after 10 days consult your doctor or pharmacist' will be included on the larger pack sizes for the 60mg and 120mg products to ensure that consumers stop taking this product after 10 days (similar to the current fexofenadine hydrochloride 60mg and 120mg lower pack size warning on the general sale packs but with a longer duration of use) as they may not be experienced users or who have not previously used fexofenadine. This statement will be included in order to mitigate the potential risk of misdiagnosis of any underlying serious condition they may have. All the other additional statements included in red will be included on par with the existing fexofenadine 60mg and 120mg general sale packs that have been Medsafe approved and provided for reference in Appendix 1.

The carton label will also have the signal header removed to reflect the new classification.

Fexofenadine 180mg small pack size:

As stated above for the fexofenadine 60mg and 120mg larger pack sizes the only changes to the labeling for the current 180 mg packet will be the removal of the signal warning Pharmacy Only and the pack size will be 5 tablets. There are no changes proposed to the formulation and dosage instructions.

The labelling and packaging of the 180 mg presentation will also include appropriate warning statements as per the fexofenadine presentations currently exempt from classification as Pharmacy-Only (Telfast 60 mg and 120 mg tablets) such as information stated in Table 9 above. The statement 'Do not use for more than 5 days. If symptoms persist after 5 days consult your doctor or pharmacist' will be included on the small pack to ensure that consumers do not take this product after 5 days consistent with the amount of tablets available in the pack for a once daily dose for no more than 5 days. This statement will be included in order to mitigate the potential risk of misdiagnosis of any underlying serious condition they may have. This will ensure that medical advice is sought by less experienced or first time users where symptoms persist despite treatment.

All the other additional statements included in the table above in red will be included on par with the existing fexofenadine 60mg and 120mg General Sale packs that have been Medsafe approved and provided for reference in Appendix 1.

As the current labelling statements remain appropriate to mitigate any potential risks, the proposed increase in pack size for fexofenadine 60mg and 120mg and the proposed 180mg small pack size will not decrease the established safety of fexofenadine for the treatment of SAR.

14 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, 120mg or 180mg registered in New Zealand is displayed in Table 10 below.

Table 10 - Products containing fexofenadine hydrochloride 60mg, 120mg or 180mg in NZ

Product	Sponsor	Status
APOHEALTH Fexofenadine (see APOHEALTH Fexofenadine 180 Hayfever & Allergy Relief Film coated tablet, 180 mg (Pharmacy only))	Apotex NZ Ltd	Not available
APOHEALTH Fexofenadine 120 Hayfever & Allergy Relief Film coated tablet, 120 mg (General sale)	Apotex NZ Ltd	Not available
APOHEALTH Fexofenadine 120 Hayfever & Allergy Relief Film coated tablet, 120 mg (Pharmacy only)	Apotex NZ Ltd	Not available
APOHEALTH Fexofenadine 180 Hayfever & Allergy Relief Film coated tablet, 180 mg (Pharmacy only)	Apotex NZ Ltd	Not available
Fexaclear Film coated tablet, 120 mg (Pharmacy only)	Dr Reddy's New Zealand Limited	Consent given
Fexaclear Film coated tablet, 120 mg (General sale)	Dr Reddy's New Zealand Limited	Consent given
Fexaclear Film coated tablet, 180 mg (Pharmacy only)	Dr Reddy's New Zealand Limited	Consent given
Fexofast 120 Tablet, 120 mg (Pharmacy only)	Teva Pharma (New Zealand) Limited	Consent given
Fexofast 180 Tablet, 180 mg (Pharmacy only)	Teva Pharma (New Zealand) Limited	Consent given
Fexofenadine Film coated tablet, 120 mg (Pharmacy only)	Douglas Pharmaceuticals Limited	Not available
Fexofenadine Film coated tablet, 120 mg, Rex (Pharmacy only)	REX Medical Ltd	Consent given
Product	Sponsor	Status
Fexofenadine Film coated tablet, 180 mg (Pharmacy only)	Douglas Pharmaceuticals Limited	Not available

Product	Sponsor	Status
Fexofenadine Film coated tablet, 180 mg, Rex (Pharmacy only)	REX Medical Ltd	Consent given
Fexofenadine Hayfever & Allergy Relief Film coated tablet, 180 mg, Pharmacy Health (Pharmacy only)	PSM Healthcare Ltd trading as API Consumer Brands	Consent given
Hayfexo Film coated tablet, 120 mg (Pharmacy only)	Dr Reddy's New Zealand Limited	Consent given
Hayfexo Film coated tablet, 180 mg (Pharmacy only)	Dr Reddy's New Zealand Limited	Consent given
Medreich Fexofenadine Film coated tablet, 120 mg (General sale)	Medreich New Zealand Limited	Consent given
Medreich Fexofenadine Film coated tablet, 120 mg (Pharmacy only)	Medreich New Zealand Limited	Consent given
Medreich Fexofenadine Film coated tablet, 180 mg (Pharmacy only)	Medreich New Zealand Limited	Consent given
Medreich Fexofenadine Film coated tablet, 60 mg (General sale)	Medreich New Zealand Limited	Consent given
Medreich Fexofenadine Film coated tablet, 60 mg (Pharmacy only)	Medreich New Zealand Limited	Consent given
Telfast Film coated tablet, 120 mg (Pharmacy only)	sanofi-aventis new zealand limited	Consent given
Telfast Film coated tablet, 180 mg (Pharmacy only)	sanofi-aventis new zealand limited	Consent given
Telfast Film coated tablet, 60 mg (Pharmacy only)	sanofi-aventis new zealand limited	Consent given
Telfast Tablet, 120 mg (General sale)	sanofi-aventis new zealand limited	Consent given
Telfast Tablet, 60 mg (General sale)	sanofi-aventis new zealand limited	Consent given
Xergic Film coated tablet, 120 mg, New Formulation (Pharmacy only)	Mylan New Zealand Ltd	Not available
Xergic Film coated tablet, 180 mg, New Formulation (Pharmacy only)	Mylan New Zealand Ltd	Not available

Product	Sponsor	Status
Xergic 180 Film coated tablet, 180 mg, . (Pharmacy only)	Mylan New Zealand Ltd	Not available

PART B REASONS FOR REQUESTING CLASSIFICATION CHANGE INCLUDING BENEFIT-RISK ANALYSIS.

1 INDICATIONS AND DOSE

What is the medicine indicated for, and for which indication(s) is the reclassification application for?

Fexofenadine hydrochloride is indicated for seasonal allergic rhinitis (SAR) for adults and children 12 years of age and over. SAR is a condition suitable for diagnosis and self- management by the consumer.

The reclassification application is to increase the pack size allowance in grocery channels of the fexofenadine hydrochloride 60mg and 120mg dosage units and to include a small pack size of the fexofenadine hydrochloride 180mg dosage units as per the proposal below:

'for the treatment of seasonal allergic rhinitis in adults and children 12 years of age and over when in capsules containing 60 milligrams or less of fexofenadine hydrochloride or in tablets containing 120 milligrams or less of fexofenadine hydrochloride with a maximum daily dose of 120 milligrams when sold in the manufacturer's original pack containing 20~~10~~ dosage units or less and not more than 10 ~~5~~ days' supply or in tablets containing 180mg or less of fexofenadine hydrochloride with a maximum daily dose of 180mg when sold in the manufacturer's original pack containing 5 dosage units or less and not more than 5 days supply.'

What is the dose and dose frequency of the medicine for this indication:

Fexofenadine 60mg can be take twice a day as required with a maximum daily dose of 120mg whilst Fexofenadine 120mg can be taken once a day as required with a maximum daily dose of 120mg for the treatment of seasonal allergic rhinitis in adults and children 12 years of age and over.

Fexofenadine 180mg can be taken once a day as required with a maximum daily dose of 180mg for the treatment of seasonal allergic rhinitis in adults and children 12 years of age and over.
It is also indicated for the treatment of urticaria in adults and children 12 years and over; however for the purpose of this reclassification this is provided for information only.

What is the evidence that the proposed indication is an OTC indication i.e., that the diagnosis and treatment can be understood by the consumer; that the risks of inappropriate treatment can be minimised?

Fexofenadine (for oral use) is already classified as a non-prescription (OTC) medicine in New Zealand _ Medsafe Classification database. It is already available as a General sale medicine in packs containing no more than 10 tablets (5 days supply). The medicine is intended for treatment of SAR, symptoms of which are clearly mentioned on the label of the medicine. The patient can then match their condition and symptoms with those on the medicine label and can easily and correctly take the medicine.

In addition SAR has characteristic symptoms and is readily distinguishable from other forms of rhinitis due to its characteristic seasonal onset. It is a self-limiting condition recognised as being appropriate for self-diagnosis. Patients seeking relief from SAR are usually highly knowledgeable on their condition.

Also risks from inadvertent use due to misdiagnosis such as symptoms of the common cold are negligible and any risks are mitigated by appropriate labeling statements. There is little risk that more serious underlying conditions will be masked or the natural course of disease progression will be altered in a substantive way as a result of treatment.

The proposed increase in pack size for fexofenadine hydrochloride 60mg and 120mg tablets as well as the proposed fexofenadine hydrochloride 180mg tablets smaller pack size (maximum 5 dosage units) will not increase the risk of misdiagnosis or suitability of the condition for self-management.

What is the treatment population for the indication (i.e. age, gender, etc.)?

The treatment population for the indication is:
Adults and Children (12 years and over)

2 PRESENTATION

What is the proposed dose form and strength of the medicine to be classified? Is this the same for all indications?

The current dosage, formulation, labelling and packaging for general sale fexofenadine supplied as fexofenadine hydrochloride 60mg, 120mg tablets remains unchanged, other than additional tablet blister strips being included in a larger size carton for the proposed pack size increase. The fexofenadine hydrochloride 180mg tablets will also remain unchanged in terms of the dosage

form, dosing, formulation and strength other than the addition of the 5 pack size in a smaller size carton.

The indication for both the fexofenadine hydrochloride 60mg, 120mg tablets larger pack size and the fexofenadine hydrochloride 180mg tablets smaller pack size will be the same: for the relief of symptoms associated with seasonal allergic rhinitis in adults and children 12 years of age and over.

To ensure that the indication is clear to the consumers for the proposed larger pack sizes of the fexofenadine hydrochloride 60mg, 120mg and the small pack of the fexofenadine hydrochloride 180mg we will ensure the following:

- quality use of the medicine will be achieved by appropriate packaging and labelling
- potential risks will be identified and managed by a consumer through appropriate labelling statements
- information in relation to use in pregnancy and breastfeeding will be included on the packaging and the risks posed by fexofenadine are no greater than those of other products such as pain relief medications that are widely available through grocery channels
- pack labelling will ensure that consumers are directed to seek advice from a healthcare professional in the event no improvement is observed within the specified timeframe on the label. This will ensure that medical advice is sought by less experienced or first-time users where symptoms persist despite treatment.
- The proposed fexofenadine hydrochloride 60mg, 120mg tablets larger pack size and the fexofenadine hydrochloride 180mg smaller pack size will not decrease safety in use of fexofenadine hydrochloride considering the wide therapeutic index and the current labelling statements remain appropriate to mitigate any potential risks.

What disposal considerations need to be made for the medicine?

No special disposal considerations are required for this medicine.

How practical and easy to use is the proposed presentation?

The proposed presentation is patient-friendly and convenient to use. The tablets are packed in a blister. Each tablet can be easily pulled out of the blister without affecting the integrity of the other tablets in the blister. This presentation is effectively already available for supply in grocery outlets and the change will only increase the 60mg and 120mg pack size as well as introduce a 180mg small pack size in the grocery channels.

3 CONSUMER BENEFITS

This application seeks to increase the pack size in general sale of the 60mg and 120mg fexofenadine dosage units when used in adults and children 12 years of age and over for the

treatment of seasonal allergic rhinitis , when supplied in packs labelled with a recommended daily dose not exceeding 120mg to allow a maximum of 10 days' supply. We also seek to include in general sale the fexofenadine hydrochloride tablets containing 180mg or less of fexofenadine hydrochloride with a maximum daily dose of 180mg when sold in the manufacturer's original pack containing 5 dosage units or less and not more than 5 days' supply.

What is the history of this medicine's use for the proposed indication(s) (ie, number of users, number of countries used in)?

Fexofenadine hydrochloride products are used worldwide in over 120 countries, with cumulative exposures over a 13 year period indicating an estimated 44.2 million patient-years of treatment with fexofenadine. The latest Periodic Risk Benefit Evaluation Reports for the period 12 March 2012 to 11 March 2017 (8) and more recently from 12 March 2018 to 11 March 2019 (9) reveal no concerns with the product and that the safety information is generally consistent with the known safety profile of fexofenadine and is comparable to that of other products in this therapeutic class. This confirms that the risk profile of the medicine is well defined and the medicine is substantially safe for use.

Finally fexofenadine hydrochloride 60mg and 120mg tablets are available in New Zealand as General Sale medicines following the gazettal on the 11th of February 2010. (10)

To what extent is this medicine used for the proposed indication(s) (ie duration of use, frequency of use)?

Fexofenadine is an effective seasonal allergic rhinitis (SAR) treatment option, proven to improve the quality of life of SAR patients.

Fexofenadine is a non-sedating antihistamine which effectively relieves the symptoms of SAR (11)

It has a rapid onset and long duration of action either 12 hour (60mg) or 24 hour (120mg or 180mg) following administration of a single tablet. The 60mg tablet can be taken twice daily as required. The 120mg tablet can be taken once daily as required. The 180mg tablet can also be taken once daily as required. (12)

Fexofenadine hydrochloride 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 and contraindications 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.

What is the evidence that improved access is beneficial for the individual?

With better access to the medication, consumers will be able to take care of their allergic symptoms in a more efficient way. Despite severe symptoms, people with allergic rhinitis tend not to seek medical advice regarding treatment. Increasing the availability of this medicine in general sales will improve the consumers involvement in their health.

Also currently within the pharmacy channels the fexofenadine hydrochloride larger pack sizes of the 60mg and 120 mg tablets and the fexofenadine hydrochloride 180mg tablets are experiencing particularly an ongoing demand for Telfast 60mg tablets 20s pack size, Telfast 120mg tablets 10s pack size and Telfast 180mg tablets 10's size as per Table 5 in PART A Section 10 which also indicates that pharmacy channels remains the key outlet for consumers seeking longer term management options, particularly those who are chronic sufferers.

The classical symptoms of SAR can have a significant impact on peoples' lives (13) and they are physically distressing and cause considerable psychological and social distress to an individual. It can affect sleep, work performance, learning ability and participation in social activity. Allergic rhinitis often co-exists with asthma, eczema, conjunctivitis and other sinus conditions. They are readily distinguishable from other forms of rhinitis due to the characteristic seasonal onset. Typically, patients seeking relief from SAR are usually highly knowledgeable on their self-limiting condition and are capable of self-managing their course of treatment. Thus, fexofenadine is available as OTC as both Pharmacy Only and Exempt from Classification depending on pack size and dosage unit.

The availability of the 180 mg dosage unit strength in up to 5 days' supply and the larger pack sizes of the 60mg and 120 mg dosage units for no more than 10 days' supply outside of the pharmacy sales environment will allow more flexible access for those sufferers living in remote areas or for patients whose lifestyle patterns makes access to a pharmacy within business hours highly challenging. Also the cost of treating this condition and indirect costs related to loss of workplace productivity resulting from the disease are substantial. It is a significant cause of lost work and school days for patients. Hence, easy availability of this medicine in general sales will enable the patients to start the medicine as soon as the symptoms get noticed and increasing the range of available strengths and pack sizes which would lessen the requirement for the patient to revisit the purchase point.

As per above evidence improved access to fexofenadine hydrochloride 60mg and 120mg larger pack sizes and the availability of the 180mg small pack size will be beneficial to the individual allergy sufferer.

What are the benefits from a consumer viewpoint and what is the evidence of improved consumer involvement in their health?

The symptoms of SAR being treated with fexofenadine are easily identifiable, and as discussed above, it has been well established sufferers are highly capable of self-diagnosis and self-management. There is a medically justified need for SAR sufferers to have immediate access to treatments that will allow them to manage symptoms that have an acute onset and significantly impact quality of life.

The larger pack sizes of the 60mg and 120 mg dosage units for no more than 10 days' supply will meet the needs of those consumers who seek access to therapy 'as required' and wish to obtain more than 5 days' supply. This may include short term treatment of multiple family members, using a more portable pack size for travel or work purposes as a 'top up' or to be 'on hand' to be able to relieve symptoms immediately upon exposure to a trigger that is experienced or those sufferers experiencing intermittent episodes over a longer period. The ability to purchase a larger pack size would thus support user convenience and decrease the economic burden of SAR.

Also the availability of the 180mg dosage unit for up to 5 days' supply will support those sufferers requiring ready access to a higher strength product in a smaller convenient pack size to self-manage their condition. The symptoms treated by fexofenadine are generally unrelated to serious conditions and are unlikely to mask a more sinister underlying condition.

4 CONTRAINDICATIONS AND PRECAUTIONS

What are the contraindications for the medicine and how easy are they to identify and prevent?

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

What are the precautions for this medicine and how easy are these to understand?

There are only a number of precautions to be undertaken and these can be easily to understand. 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.

As with most new drugs there is only limited data in the elderly and renally or hepatically impaired patients. Fexofenadine hydrochloride should be administered with care in these special groups and this is covered in the Datasheet (12) as well as the Consumer Medicine Information (14). No warnings are included on the actual cartons due to the limited data availability.

The label would include a number of precautions (words to the effect) in line with the NZ Label Statements Database for Fexofenadine as per below and by including these statements this would ensure that the patient easily understands the warnings:

- Do not use in children under 12 years old.
- Do not use for more than 5 days at a time. If symptoms persist after 5 days consult your doctor or pharmacist. (applicable to the 180mg product) or Do not use for more than 10 days at a time. If symptoms persist after 10 days consult your doctor or pharmacist (applicable to the 60mg and 120mg larger pack sizes)
- Do not use with other antihistamines.
- Do not use if you are pregnant unless advised by a doctor or pharmacist.
- Do not use if you are breastfeeding unless advised by a doctor or 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.

Does the medicine have a low therapeutic index?

No, Fexofenadine in fact has a wide therapeutic index rendering it safe & efficacious in variety of doses. Fexofenadine being the second generation H1 antihistamine has broader dose range efficacious whilst having a favourable adverse event profile. According to the 2003 CONGA recommendations authored by Holgate et.al Fexofenadine is considered to have the best therapeutic index as in subjective and objective tests it is devoid of sedation even when the subjects were given three to four times the recommended doses. (15)(16)

What class effects need to be considered and what are the risks?

The second generation antihistamines are resultant of the significant side-effect arising from the older/first generation antihistamines. Fexofenadine, being second generation antihistamine is also termed non-sedating because it does not cross the blood-brain barrier appreciably. This is due to their decreased lipophilicity and because they are substrates of P-glycoprotein, which pumps them out of the blood-brain barrier capillary endothelial cells and back into the capillary lumen. The second-generation H1 antagonists have no effect on muscarinic receptors. All first-generation and most second-generation H1 antagonists are metabolized by CYPs and little, if any, is excreted unchanged in the urine; most appears there as metabolites. Exceptions are cetirizine and acrivastine (<40% metabolized) and fexofenadine, levocetirizine, and epinastine (<10% metabolized). Cetirizine, levocetirizine, and acrivastine are excreted primarily into the urine; fexofenadine is mainly excreted in the faeces, and epinastine is excreted in both urine (55%) and faeces (30%). (17)

What are the risks of the medicine being used in an OTC environment?

Fexofenadine is already available as an over-the-counter medicine in New Zealand, hence there is no risk of the proposed reclassifications. The relative risk is for increasing the 60mg and 120mg pack size. In Pharmacy large pack sizes up to 70 tablets for Telfast 180mg, 30 for Telfast 120mg and 20 for Telfast 60mg are already available so the overall risk profile is not expected to change by increasing the 60mg and 120mg pack size to 10 days' supply from 5 days' supply worth of tablets. The successful reclassification of the fexofenadine from Pharmacy Medicine to General sale in 2009 (6) has demonstrated that the risks of misdiagnosis or the potential to mask an underlying condition is therefore minimal. The proposed 60mg and 120mg larger pack sizes and the proposed 180mg small pack size will also retain all the warning statements required for fexofenadine to be sold as a General sale medicine. In addition, it should be noted that loratadine is already available in larger packs of 10's without any problems being evident. The risk:benefit ratio is not significantly different for loratadine in comparison with fexofenadine.

What other drug interactions need to be considered?

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 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. (12)

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.

What food and / or drink interactions need to be considered?

Fexofenadine may be administered without regard to food because food does not affect the extent of absorption of the drug when administered as conventional tablets. Antacids containing aluminium and magnesium hydroxide have reduced the absorption of fexofenadine. Fruit juices including grapefruit may reduce the bioavailability of fexofenadine and use together should be avoided. (11)

Are there any other restrictions when taking the medicine (ie, driving restrictions or operating machinery)?

As drowsiness has been reported in some individuals in placebo controlled clinical trials involving seasonal allergic rhinitis and chronic idiopathic patients should be warned that although this medicine is unlikely to affect their ability to drive or operate machinery, a few people may be impaired and care should be taken; however this is clearly addressed through including a warning on the label so this is clear to the consumer (refer to Appendix 1 for the proposed labels). In addition it is worth noting that in Australia the TGA's Scheduling Delegate's interim decisions and reasons for decisions (1)(2)(3), it was noted the advice to the TGA's delegate was that Fexofenadine had a notable lack of sedative effects, low abuse potential, has a wide therapeutic index and a well-established toxicity profile; therefore the above mentioned restriction would be considered minor in nature for the fexofenadine hydrochloride 60mg and 120mg larger pack size proposal and the fexofenadine hydrochloride180mg small pack size proposal in the general sale channels.

Are there any special populations where exposure to the medicine needs to be restricted?

Administration in renal impairment – According to Martindale (11) the US licensed product information recommends that initial oral doses of fexofenadine hydrochloride in adults with renal impairment should be reduced to 60 mg once daily. In children with renal impairment, the initial dose should be reduced to 30 mg once daily in patients aged 2 to 11 years, and to 15 mg once daily in children aged 6 months to less than 2 years. UK product information advises that fexofenadine should be given with caution to patients with renal impairment; however, it also states that dose adjustment is not considered to be necessary in such patients.

In similar ways, the NZ Datasheet (12) details that 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. As with most new drugs there is only limited data in the elderly and renally or hepatically impaired patients. Fexofenadine hydrochloride should be administered with care in these special groups.

Breast feeding According to Martindale (11) -no adverse effects have been seen in breast-fed infants whose mothers were receiving fexofenadine, and the American Academy of Pediatrics

considers that it is therefore usually compatible with breast feeding. In pregnancy, according to the NZ Datasheet, there are no studies in pregnant women exposed to fexofenadine hydrochloride alone or through the administration of terfenadine. As with other medications, Telfast should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. There are no studies of Telfast in lactating women. Telfast 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.

5 UNDESIRABLE EFFECTS

What are the known undesirable effects and the frequencies of these? Do these vary for special populations? Are these reversible or treatable?

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. (12)

There has been no reports published since distribution from grocery channels began that indicates there has been any change in the safety profile compared to the long term experience from many years of use in countries around the world including the USA that has a significantly larger population base than Australia or New Zealand and where larger pack sizes and higher strengths of fexofenadine are available.

The number of adverse event reports recorded on the Medicine Adverse Reaction Reporting SMARS Database in New Zealand for the periods pre and post the availability of unscheduled fexofenadine (June 2006- September 2010 and September 2010 till June 2020) are as follows:

Table 11 - Number of Adverse Event Reports on the NZ SMARS database for the periods pre (June 2006 – September 2010) and post (Oct 2010- December 2020)

	Number of adverse event cases
	Fexofenadine
Jun 2006-Sep 2010	10 reactions (5 reports)
Sep 2010- June 2020	16 reactions (20 reports)

Post-Marketing Surveillance:

The latest Periodic Risk Benefit Evaluation Reports for the period 12 March 2012 to 11 March 2017 (8) and more recently from 12 March 2018 to 11 March 2019 (9) reveal no concerns with the product and that the safety information is generally consistent with the known safety profile of

fexofenadine and is comparable to that of other products in this therapeutic class. The current cumulative exposure from January 2002 to September 2018, calculated in patient years is 44.2 million(9)(8). Interrogation of the FAERS database run for fexofenadine and fexofenadine hydrochloride described approximately 20,000 AE cases reported for the period 1996 – 2018 (Appendix 2), an extremely low figure given the global exposure of the product.

Second generation antihistamines including fexofenadine are a class of drugs that have been recognised globally as safe and effective. Fexofenadine is considered low risk and has a similar efficacy profile as loratadine and cetirizine. Given fexofenadine has similar indications and fewer side effects, there is low risk to the consumer of the 60mg and 120mg larger pack size as well as the180 mg strength in the proposed small pack size for adults and children over 12, for general sale.

What are the risks and consequences of known undesirable effects?

As described above, majority of the adverse effects are mild and do not pose any serious risk. These again are not seen to be significantly different from loratadine which is already available in packs for 10 days' supply from grocery channels.

Are there any significant safety concerns for the medicine under review?

There are no known significant safety concerns of the known undesirable effects due to the lack of toxicity and favourable safety profile of fexofenadine which has been well established via numerous preclinical and clinical studies at and above the recommended 180 mg per day dose. The maximum single dose tested in clinical trials is 800 mg in six healthy subjects. In a multiple-dose study, doses of 690 mg every 12 hours for 28.5 days were given to three healthy subjects and, in another study with forty subjects, a dose of 400 mg every 12 hours was given for 6.5 days. No clinically significant adverse events were reported in these studies. (18)(19)(20)

Have there ever been any withdrawals of the medicine or other regulatory actions taken for safety reasons (during a time period or in a specific jurisdiction)?

We confirm that there were no withdrawals or regulatory actions of the medicine for safety reasons.

Are there any withdrawal effects following cessation of use of the medicine?

No, since the drug does not lead to dependence, cessation of fexofenadine has not been reported to cause any withdrawal symptoms. Recurrence of the symptoms; however may occur which may require consultation from a health care professional.

6 OVERDOSE

Is there a potential for overdose of the medicine?

There is no clinical experience with a fexofenadine overdose. In healthy volunteers, single doses of fexofenadine HCl up to 800 mg and multiple doses up to 690 mg twice daily for 28.5 days resulted in a cardiac safety profile similar to that of placebo. (18)(19)(20) Furthermore, in a long-term safety study in which patients received fexofenadine HCl 240 mg once a day for 12 months, no electrocardiogram changes were observed compared with placebo, and no cardiac adverse events were reported (21). Also in clinical trials with SAR and chronic idiopathic urticaria patients, no electrocardiogram changes have been reported with fexofenadine treatment at recommended or supratherapeutic doses relative to placebo. (12)(11)

Finally as each tablet is individually packed in a blister, the likelihood of an overdose is low when compared to a bottle. This is also mitigated though clear dosing instructions on the pack. (Appendix 1)

Are there any reports of overdose of the medicine and what are the consequences of overdose of the medicine?

Most reports of fexofenadine hydrochloride overdose contain limited information. However, dizziness, drowsiness and dry mouth have been reported. As stated above single doses up to 800mg and doses up to 690mg twice daily for 1 month were studied in healthy subjects without the development of clinically significant adverse events. Also 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 2,000mg/kg. In the case of an overdose, standard measures to remove any unabsorbed drug would have to be employed. Symptomatic and supportive treatment is recommended. There has been no reported case of an acute overdose of fexofenadine hydrochloride. In the event of an overdose the standard practice would be to contact the National Poisons Centre on 0800 POISON (0800 764766).(12)

7 MEDICATION ERRORS AND ABUSE/MISUSE POTENTIAL

Would reclassification affect the risk of unnecessary use and what are the reported cases of abuse/misuse/accidental overdose?

Fexofenadine has been available in New Zealand since June 1997 and in Australia since February 1997. Fexofenadine 60mg and 120mg smaller pack sizes for the treatment of SAR in adults and children 12 years of age and over with a maximum daily dose of 120 milligrams containing 10

dosage units or less and not more than 5 days' supply have been available in the grocery channels in New Zealand since late 2010 (following the gazettal on the 11th of February 2010). Moreover, 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.

There is a possibility that a patient displaying common cold symptoms may think that they have SAR.

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 strength, 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 clearly differentiated labelling of the strengths, the doses and pack sizes as well as clear instructions on the pack will therefore limit the use of the product (refer to Appendix 1 for the proposed labels).

Moreover, patients will be instructed to consult a healthcare professional 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.

What are the reported medication errors post-market?

As the medicine is supplied as a unit-dose blister pack, the chances of medication error is low and increasing the 60mg and 120mg pack size as well as including the 180mg small pack size in grocery channels would unlikely cause a medication error.

How would reclassification affect import considerations?

Reclassification would not affect import considerations.

What is the addiction potential of the medicine?

Given that fexofenadine has a favourable safety profile there are no reports of addiction of this medicine. The cases of accidental overdose/medication errors have been discussed above. Accidental overdose is more likely in paediatric patients taking liquid formulations of fexofenadine hydrochloride and the proposed two reclassifications are not intended for paediatric patients.

In summary, the proposed increase in pack size of the fexofenadine 60mg and 120mg dosage units and the proposed small pack size of the fexofenadine 180mg will not increase the potential for abuse/misuse particularly considering a wide range of pack sizes including larger pack sizes and a broad range of strengths of fexofenadine are available for self-selection through pharmacy channels.

8 COMMUNAL HARM AND/OR BENEFIT

What are the possibilities of community harm resulting from wider use of the medicine in question

There is no possibility of community harm from wider use of the medicine.

What are the possibilities of community benefit resulting from wider use of the medicine in question

Since the availability of unscheduled fexofenadine for the treatment of SAR, sales data indicate a strong demand from grocery channels, recognizing that the majority of purchasers are experienced users who are highly knowledgeable on their symptoms and treatment choice. As shown in Part A Section 10 Table 5 and Table 6 strong sales (within pharmacy) of the 120mg x10 tablet pack, the 60mg x 20 pack as well as the strong sales of the current Telfast 180mg x 10 pack size tablet reflects the medical need of sufferers and this can be supported via improved access to medication to relieve symptoms which are a significant burden on daily living. (13)

There is no change to the intended use of unclassified fexofenadine as a result of this application. The use of fexofenadine as a safe and effective treatment for SAR has been established based on more than twenty years of use in over 120 countries worldwide. There has been no evidence of a change in safety profile identified from routine post-marketing surveillance following the substance being made available for self-selection by consumers in grocery channels in any country worldwide. A copy of the latest PBRER is provided as part of the supporting data. (9)(8)

In addition we would like to highlight that in the USA, which has a significantly larger population base than New Zealand or Australia, fexofenadine has been available via grocery channels for around 8 years in larger pack sizes and at the higher strength of 180mg fexofenadine. This strongly supports the favourable benefit/risk profile of the proposed increase in pack sizes of Telfast tablets containing either 20 x 60mg or 10x 120mg fexofenadine as well as the introduction of a higher strength 180mg fexofenadine small pack size in New Zealand.

Fexofenadine has also been shown to be safe at doses of 800 mg/day, 6 times the recommended daily dose for SAR, with no clinically significant adverse events reported from 40 patients treated for 6.5 days (18) .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. Thus should a consumer accidently consume an entire pack of Telfast 180mg containing 5 tablets amounting to 900mg or Telfast 120mg containing 10 tablets amounting to 1200mg of fexofenadine, there is minimal risk of adverse sequelae. Thereby there is no additional toxicity or safety risk based on the proposed increase in pack sizes of the fexofenadine hydrochloride 60mg and 120mg dosage units and the proposal of the small pack size of fexofenadine hydrochloride 180mg dosage units to become general sale medicines.

In summary, the proposed changes to increase in pack size of the fexofenadine hydrochloride 60mg and 120mg and the small pack size of fexofenadine hydrochloride 180mg dosage units will provide an additional benefit through providing a broader access to this medicine which will lead the consumers seeking more flexible and convenient treatment options without any risk of changing the favourable benefit/risk profile; which will therefore not impose any greater risk to the population than the current Pharmacy Only Medicine classification.

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. 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 relationship between patients worst symptoms and usual pharmacy trading hours, we 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.

9 INTEGRATED BENEFIT-RISK STATEMENT

A summary of the reclassification benefits

SAR can have a bad effect on patients' quality of life. The symptoms of SAR include sneezing, itching, watery eyes and runny nose. These symptoms typically occur in seasonal times such as in spring and autumn and this may lead to sleep disturbance, less activity, and other problems. The cost of treating this condition as well as the indirect costs related to loss of workplace productivity resulting from the disease are substantial. It is also a significant cause of lost work and school days for patients. Despite severe symptoms, people with allergic rhinitis tend not to seek medical advice regarding treatment.

Currently, fexofenadine is pharmacy only when for oral use except for the treatment of seasonal allergic rhinitis in adults and children 12 years of age and over when in capsules containing 60 milligrams or less of fexofenadine hydrochloride or in tablets containing 120 milligrams or less of fexofenadine hydrochloride with a maximum daily dose of 120 milligrams when sold in the manufacturer's original pack containing 10 dosage units or less and not more than 5 days' supply.

On average in New Zealand pharmacy operating hours are generally short compared to the operating hours of supermarkets. (22) This can limit the access of SAR patients to required medication and/or additionally decrease access by requiring more frequent trips to purchase medicine. This application seeks the reclassification fexofenadine hydrochloride 60mg and 120mg in larger pack sizes (up to 10 days' supply) and fexofenadine hydrochloride 180mg in smaller pack size of no more than 5 tablets for up to 5 days' supply to a General Sale Medicine. This will provide patients easier and more convenient access to an effective and safe short-term therapy. It is further noted that this is entirely consistent with the other common antihistamine, loratadine which has been in place for some time now.

The favourable safety profile of fexofenadine for adults and children 12 years of age and over has been well established and has been reviewed by regulatory agencies globally. Fexofenadine is a widely used over-the-counter (OTC) product in the US, Canada and EU. In Australia the TGA's Scheduling Delegate's interim decisions and reasons for decisions, 1.7 Fexofenadine (3) and September 2016: 1.2 Fexofenadine (1)(2), it was noted the advice to the TGA's delegate was that fexofenadine had a notable lack of sedative effects, low abuse potential, has a wide therapeutic index and a well-established toxicity profile, not associated with significant ECG abnormalities. There was no significant increase in risk with increased dose from 120mg/day to 180mg/day and the safety profile is well defined and fexofenadine is safe for use at doses at 800 mg/day, six times the dose recommended for treatment of SAR.

In addition it was noted in the reasons for the interim decision made on 10 June 2020 (3) for the fexofenadine hydrochloride 180mg small pack size proposal that the benefit of broadening the

availability of fexofenadine for general sale to 180mg tablets (5 days supply) for people aged over 12 years outweighs potential risks of improper use and that seasonal allergic rhinitis is a common, easily identified condition that is appropriate for self-management where non-treatment can affect a sufferer's quality of life. Also support of the 180 mg strength in the general sales environment is provided by clinical studies on the safety and efficacy of fexofenadine at the 120 mg and 180 mg strengths compared with cetirizine 10 mg, as assessed by mean 24 hour total allergy symptom scores (TSS) and adverse events (AE). (23)(16)

Cetirizine is a second generation antihistamine currently approved for the relief of SAR symptoms and available as general sale for adults and children over 12 when in a pack no more than 10 days' supply and a daily dose not exceeding 10 mg. The efficacy of both fexofenadine strengths was comparable to the 10 mg cetirizine, however assessment of drowsiness and the combined drowsiness and fatigue was statically significantly higher in the cetirizine treatment group. In addition, patients receiving 180 mg fexofenadine reported improvements in SAR symptoms relief associated with less drowsiness compared with the 10 mg cetirizine treatment group and improvement in motivation scores, suggesting the 180 mg fexofenadine treatment of SAR may benefit the subjective malaise often reported during the allergy season. (16). Both studies show a decrease in the AEs reported confirming that 180 mg fexofenadine compared with cetirizine supports no greater risk of 180 mg available as general sale to the currently available cetirizine at 10 days' supply.

A summary of the reclassification risk of harm

No harm to the consumer/ patient is expected as a result of this reclassification.

A summary of the need for the medicine at the classification proposed

There is growing evidence to prove the increase in prevalence of allergic conditions including seasonal allergic rhinitis recently. (7)(13)

It is estimated that approximately 20% of the New Zealand population suffers from allergic rhinitis. (7). According to the Best Practice Advocacy Centre SAR may affect up to 30% of adults and 40% of children. (13) Prevalence is higher in Western countries including New Zealand, Australia, Canada, USA and UK. The symptoms of SAR being treated with fexofenadine are easily identifiable, and as previously discussed, it has been well established sufferers are highly capable of self-diagnosis and self-management. There is a medically justified need for SAR sufferers to have immediate access to treatments that will allow them to manage symptoms that have an acute onset and significantly impact quality of life. The proposed increase in pack sizes for fexofenadine hydrochloride 60mg and 120mg dosage units and the increase in strength for fexofenadine hydrochloride 180mg dosage units will support those sufferers requiring ready access to a wide range of fexofenadine hydrochloride containing products whether it is a larger pack size of the 60mg or 120mg or a higher strength 180mg product in a smaller convenient pack size to self-manage their condition and to reduce the need of consulting a healthcare professional. The symptoms treated by fexofenadine are generally unrelated to serious conditions and are unlikely to mask a more sinister underlying condition.

To minimise potential risks of the availability in the general sale space, the number of days of supply or number of units will be restricted to an appropriate pack size and will be accompanied by appropriate labelling (with clear dosage instructions, warnings and indication; see Appendix 1 for the proposed labelling).

Overall the risk assessment confirms that there is no change to the safety, efficacy or quality of the product that impacts the overall risk profile as a consequence of the two proposed reclassifications. Any potential risks can be mitigated through the existing packaging and labelling statements that ensure quality use of the medicine.

Precedent – how are other medicines in the same class classified?

There is already precedence in New Zealand of second generation antihistamine products available in grocery. For example on the 56th meeting in June 2009, the NDPSC considered the scheduling of fexofenadine including a proposal to exempt fexofenadine in preparations for oral use for the short term treatment of Seasonal Allergic Rhinitis. Consideration was given at the October 2009 meeting regards to the main issue around whether a patient could self-diagnose SAR and whether it would be appropriate to have such a product for sale in a supermarket. (6)

The Committee concluded that these issues could be addressed by appropriate labels and through including warning statements such as 'do not use with other anti-histamines; this product should not be used when pregnant or when breast feeding except when advised by your Doctor or Pharmacist'. Based on these recommendations the Committee agreed to reclassify fexofenadine hydrochloride 60mg capsules, 120mg film coated tablets and 60mg film coated tablets from pharmacy-only medicine to general sale medicine for the treatment of seasonal allergic rhinitis. (6)

There are also other second generation antihistamines that need to be taken into account. According to the minutes of the 46th meeting of the MCC dated 15 November 2011 a reclassification application was put forward for cetirizine 10mg tablets from pharmacy-only medicine to general sale medicine when in packs containing sufficient tablets for only 5 days' supply and when used for Seasonal Allergic Rhinitis. It was recommended that cetirizine hydrochloride should be reclassified from pharmacy-only medicine to general sale medicine when in packs containing sufficient tablets for only 5 day's supply and when used for Seasonal Allergic Rhinitis. It was agreed that the label should reflect the wording on the loratadine.(24) We also understand that a more recent reclassification application has been put forward to reclassify cetirizine hydrochloride 10mg in packs containing no more than 10 dosage units. (24)(25)

Finally the proposed changes in the fexofenadine classification also aligns with a recent New Zealand Gazettal Notice from the 18th of August 2016 which is based on the 55th meeting of the Medicines Classification Committee held on the 3rd of May 2016 where loratadine has also been approved for General Sale use, when in divided solid dosage forms for oral use containing 10 milligrams or less per dose form for the treatment of seasonal allergic rhinitis when sold in the manufacturer's original pack containing not more than ten days' supply. (5)

Are there any risk mitigation strategies required? If so, what risk mitigation strategies are required eg, healthcare professional education; integration of care; consumer information to be provided etc?

No risk mitigation strategies are required for the 60mg and 120mg larger pack size proposed reclassification and for the proposed 180mg small pack size since the product is already available without any issues either in small pack sizes in grocery or OTC in pharmacy.

What is the evidence that these proposed risk mitigation strategies would be effective?

Not Applicable

What post-market surveillance activities would be carried out?

No particular post-marketing surveillance activities would be carried out due to the low risk nature of the proposed reclassification.

Is the proposed reclassification supported by professional bodies?

This is not applicable to this type of reclassification.

CONCLUSION

In conclusion New Zealand has one of the highest rates of allergies in the developed world and many consumers with SAR are chronic sufferers who are highly knowledgeable on their condition and treatment options. SAR is generally self-limiting; however, the symptoms have a significant impact on the daily lives of those affected. Also according to BPAC NZ, seasonal allergic rhinitis can affect sleep, work performance, learning ability and participation in social activity. It is recommended that for mild symptoms antihistamines should be tried first and they may be used as needed as they are less sedating and are less associated with anticholinergic effects. (13) Easy access to treatment to provide immediate relief of symptoms is essential for effective self-management of the condition.

Fexofenadine has been approved in over 120 countries worldwide for the relief of SAR symptoms. It has been available in New Zealand since June 1997. The current approved Datasheet (12) recommended daily dose of fexofenadine for the treatment of SAR is 120 mg and 180 mg. Relief from SAR by the recommended dosage can be achieved and can be taken as either one 60 mg tablet that provides 12 hour relief twice daily, or a single 120 or 180 mg tablet that provides 24 hours relief once daily for added convenience.

Fexofenadine is a well-established molecule with a well-defined safety profile supported by over 20 years of clinical experience and an established history of safe use by consumers in the self-management of SAR.

SAR is a condition suitable for diagnosis and self- management by the consumer and appropriate labelling is in place to ensure the patient population can take the product and ensures quality use of medicines with instructions on when to seek advice from a healthcare professional.

The proposed increase in pack size for the 60mg and 120mg fexofenadine dosage units and the proposed introduction of the fexofenadine 180mg small pack size in grocery channels will not decrease safety in use of fexofenadine considering the wide therapeutic index and the current labelling statements remain appropriate to mitigate any potential risks.

In conclusion, the benefits outweigh the risks for this expansion of the fexofenadine range in grocery for an appropriate, short term indication, duration of treatment and dose restrictions for the purpose of convenience and access to medicines for the New Zealand population without posing any greater risk than its current classification.

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