TYPE OF APPLICATION Abridged Application	
PROPOSED LICENCE HOLDER: **Marion Merrell Ltd**	
MANUFACTURER DOSAGE FORM: **Tablets 120 mg and 180 mg**	
LEGAL STATUS: POM	**SALE/SUPPLY:** Pharmacy only

Single daily dose formulations of fexofenadine, a recently licensed metabolite of terfenadine, for the existing indication of seasonal allergic rhinitis and for the new indication of urticaria.

INDEX: **Page:**

NUMBER: PL: 04425/0157-0158	
PRODUCT NAME: Telfast	
THERAPEUTIC CLASSIFICATION: **H1 histamine antagonist**	
RECEIVED: 5 July 96	
MEETING: 9 October 96	
COMMITTEE ON SAFETY OF MEDICINES	
CONSIDERATION BY OTHER COMMITTEES: None	
ASSESSED BY: Pharmacy: [redacted] Pre-Clinical: [redacted] Clinical: [redacted]	

Redacted under Section 40 of the FOI Act

MARKETING AUTHORISATION APPLICATION (ABRIDGED)

ASSESSMENT REPORT

LICENCE No.: PL: 04425/0157-0158

PROPRIETARY NAME: TELFAST

ACTIVE(S): FEXOFENADINE

COMPANY NAME: MARION MERRELL LTD

EC ARTICLE:

LEGAL STATUS: POM

PART I. INTRODUCTION AND BACKGROUND

These are abridged applications for two strengths of tablets containing fexofenadine hydrochloride. Fexofenadine is the active metabolite of terfenadine and was first licensed in tablet and capsule form in March 1996 (PL 04425/0155- capsule, 6- tablet). The original application for these products was for a 60mg product but during assessment, at the request of CSM, the product strength was reduced to 40mg and dosage reduced from 60mg twice daily to 40mg twice daily. The current applications have two purposes: the 120mg product is proposed to allow once daily dosing for seasonal allergic rhinitis and the 180mg product, also for once daily dosing, has been submitted in order to propose urticaria as a new indication. The two products have the same formulation differing only in their final mass and so pharmaceutically they have been assessed jointly.

PART II. PHARMACEUTICAL ASSESSMENT

1. Drug Substance

Fexofenadine Hydrochloride Terfenadine Hydrochloride

Cross reference is made to PL 04425/0155. This approach can be considered satisfactory in this instance but if the application is converted into a mutual recognition procedure full information must be supplied. Fexofenadine is produced [redacted]

[redacted]

2. Finished Product

Composition

The products are presented as peach coloured, capsule shaped tablets. The formulations are shown in annex 1. Tablets contain 180 and 120mg of fexofenadine hydrochloride which is equivalent to 168 and 112mg of active. All product particulars express the quantity of active as the base first followed by the quantity of salt. This was accepted for the lower strength product to comply with the requirements of current European legislation requiring the active content of products to be declared in terms of the mass of active entity. The two formulations are proportionately identical. The 180mg formulation detailed in annex 1 was used in bioequivalence studies. Tablets will be packed in PVC/PE blisters ([redacted]) and sealed with a hard tempered aluminium foil ([redacted] This differs from that used for the 40mg tablet in that the layer of PVDC has a greater density ([redacted] and by the inclusion of polyethylene. The polyethylene layer is said to be required to bind the thicker PVDC layer to the PVC.

Development Pharmaceutics

It was not possible to scale up the 40mg formulation directly for these products because of the size of the resulting tablets. The 40mg tablet formulation is also shown in annex 1. Three higher strength formulations were used for bioscreening studies indicating that all three had acceptable bioavailability. Two of these were then tested in pivotal bioequivalence studies (using the 180mg formulation) against the 60mg capsule formulation (3x60mg capsules) which was used in clinical studies. Comparative in vitro dissolution profiles are presented for the 120 and 180mg products showing them to be equivalent and so it is reasonable to extrapolate bioequivalence from the 180mg to the 120mg product. The excipients used in the formulation are unexceptional and given that they have all been used previously in the authorised 40 mg product when compatibility studies were undertaken they can be considered satisfactory.

[redacted]

[redacted]

Method of Preparation

[redacted]

[redacted]

Control of Other Ingredients

All other ingredients with the exception of pink and yellow iron oxide are controlled to either BP or Ph Eur requirements. Specifications are provided for these substances and are the same as in PL 4425/0155-6.

Packaging Materials

Specifications are outlined for the components of the strip pack and for a product of this type can be considered satisfactory.

Control Tests on Finished Product

The following specification is applied:

[redacted]

[redacted]

3. Stability

Active

[redacted]

Finished Product

[redacted]

[redacted]

Redacted under Sections 41 and 43 of the FOI Act

4. Bioequivalence Studies

Bioequivalence studies were undertaken as part of the applications for PL 04425/0155-6 showing that the 40mg capsules and tablets were bioequivalent. Identical formulations for the 60 and 40mg products and comparable dissolution profiles allowed bioequivalence between the 40 and 60mg products to be claimed. The 60mg capsule formulation was used exclusively in the clinical studies for these applications.

In a similar manner for these applications a 60mg capsule formulation was used for the clinical studies and bioequivalence studies were undertaken to demonstrate that this product (3x60mg) was bioequivalent to the tablet formulation (180mg strength). The study was an open label, randomised, six period cross over design in 27 healthy volunteers. As discussed in section 2 of this report two possible formulations proposed from development pharmaceutics were tested in this study against the 60mg product. 90% confidence intervals of the ratios of the mean AUC's for each treatment were calculated showing that both lie within the currently accepted bioequivalence range.

Comparative in vitro dissolution data is presented from the 120mg and 180mg products showing them to be equivalent allowing the demonstrated bioequivalence for the 180mg product to be applied to the 120mg also (given their identical formulations). Plasma samples are measured using HPLC/MS method that is slightly different to that used for PL's 04425/0155-6. Full details of the method have been described and validation data has been presented.

5. Product Particulars

Product labels, patient information leaflet and SPC all appear satisfactory.

6. Conclusion

[redacted]

[redacted]

[redacted]

[redacted]

Pharmaceutical Assessor
22/8/96

Annex 1.

Formulations of 40, 120 and 180mg Tablets and the 60mg Capsule

Constituent	120mg	180mg	40mg tablet	60mg capsule
Fexofenadine Hydrochoride	120mg (112mg base)	180mg (168mg base)	40mg	60mg
[redacted]				

Redacted under Section 41 and 43 of FOI Act

PART III. PRECLINICAL ASSESSMENT

INTRODUCTION

These abridged applications for Telfast 120 & 180 are for tablets containing fexofenadine hydrochloride (120 and 180 mg, respectively). Telfast 120 is indicated for relief of symptoms associated with seasonal allergic rhinitis, and Telfast 180 for relief of symptoms associated with urticaria. They are not recommended for children under 12 years. The recommended dosage for each is 1 tablet daily, representing a maximum human daily dose of 3 mg/kg for a 60 kg person taking Telfast 180 for urticaria. The previously granted licences for fexofenadine hydrochloride have a maximum daily dose of 80 mg (40 mg bid) and therefore the current applications represent an increase in dose.

A number of preclinical studies have been conducted in support of this application, and are briefly discussed in the expert report, which is appended (**Appendix 1**).

PHARMACODYNAMICS (Appendix 2)

Pharmacodynamic effects relating to the proposed indication

Fexofenadine hydrochloride (the pharmacologically active metabolite of terfenadine) is a potent selective histamine H1-receptor antagonist, and is synthesised as a racemic mixture. Two studies were submitted, one comparing the antihistaminic effects of the (-) and (+) enantiomers with that of the racemic mixture in guinea pigs with histamine-induced skin wheals, and the other comparing the effects of the enantiomers on histamine-induced contractility of isolated guinea pig ileum.

Either fexofenadine, or its (-) or (+) enantiomer, were administered to guinea pigs at doses of 0.4, 0.8, 1.6 or 3.2 mg/kg. Two hours later, histamine was injected into the anaesthetised animals. Wheal size was measured after a further 20 minutes, following sacrifice of the animals. Fexofenadine and its enantiomers all produced a dose-dependent reduction in wheal size when compared with vehicle control, but there was no difference between the three test substances.

In the isolated guinea pig ileum, both enantiomers were tested at concentrations of 0.1, 0.316 and 1 μM. Dose-response curves were shifted to the right, with a gradual flattening of the slopes at the higher concentrations. The (+) enantiomer appeared to be slightly more potent in this assay (pA_2 of 7.97 ± 0.06 compared with 7.62 ± 0.09).

General pharmacodynamic effects

No additional preclinical studies have been submitted.

Product interactions

The effects of ketoconazole and of erythromycin on the pharmacokinetics of fexofenadine have been studied using the dog as a model, and an attempt made to elucidate the possible mechanism(s) of these interactions. Ketoconazole and erythromycin both increase the bioavailability of fexofenadine in dogs, particularly when fexofenadine is administered by the oral route. The studies are discussed below.

PHARMACOKINETICS (Appendix 3)

All but one of the kinetic studies submitted were carried out to investigate drug interactions, specifically those between fexofenadine and ketoconazole or erythromycin.

Drug interactions

Biliary elimination of fexofenadine was examined in dogs before and after oral treatment with erythromycin or ketoconazole. On days 1, 6, 13 and 28 of the study, an intravenous dose of fexofenadine hydrochloride (0.5 mg/kg) was given to bile-duct cannulated Beagle dogs (2 groups of 4 males). On day 1, bile was recirculated to the duodenum following the fexofenadine dose. On day 6, bile was collected for 48 h. From day 14 to 25, animals received either ketoconazole (6.7 mg/kg once daily) or erythromycin (250 mg TID). On day 18, bile was recirculated following the fexofenadine dose, and on day 23, bile was collected for 48h.

Approximately 40% of an iv dose of fexofenadine was eliminated via biliary excretion in 48h, and 10% by renal excretion. The biliary excretion was about half of the previously reported faecal excretion, suggesting gastrointestinal secretion accounts for some of the clearance. Enterohepatic cycling was not observed.

Systemic clearance of fexofenadine was decreased by ketoconazole (by 5 to 32%), as was intestinal clearance (by 55%). Ketoconazole also decreased biliary clearance (by 27%) and increased renal clearance (by 37%), although these were less significant because they form a relatively small proportion of the systemic clearance.

Systemic clearance of fexofenadine was also decreased by erythromycin (by 23 to 30%). Biliary clearance was decreased by 73%, but erythromycin had no effect on intestinal or renal clearances.

Pretreatment of Beagle dogs (5 males) with oral ketoconazole (200 mg/day) for 6 days caused a 1.8-fold increase in plasma fexofenadine AUC_{0-24} when an iv infusion of fexofenadine hydrochloride (0.5 mg/kg) was given. When oral fexofenadine hydrochloride (2 mg/kg) was given, pretreatment with ketoconazole caused a 7-fold increase in plasma fexofenadine AUC_{0-24}. Pretreatment with oral erythromycin 250 mg TID for 5.3 days (only the morning dose given on day 2) increased plasma fexofenadine AUC_{0-24} 1.5-fold after an iv infusion of fexofenadine and 5.6-fold after an oral dose. Clearances of iv fexofenadine were about 40% lower in erythromycin or ketoconazole-treated dogs than when fexofenadine was given alone. Single doses of fexofenadine (iv or oral) did not affect steady state plasma concentrations of ketoconazole or erythromycin.

The effects of erythromycin, ketoconazole and verapamil on the permeation of fexofenadine across rat intestine was investigated in an *in vitro* intestinal diffusion model. The permeation of fexofenadine in the absorptive direction across the intestine of Sprague-Dawley rat was similar for duodenal, jejunal, ileal and colonic sections. In the jejunal and ileal sections, permeation in the secretory direction was approximately 1.5- to 5-fold greater compared to the absorptive direction, and appeared to be concentration-dependent.

Co-perfusion of fexofenadine with either verapamil or erythromycin did not affect jejunal transport in either the secretory or the absorptive direction. In the ileum, secretory transport of fexofenadine was significantly decreased by co-perfusion with either verapamil or erythromycin, whereas absorptive transport was either increased slightly (verapamil) or unaffected (erythromycin).

Ketoconazole produced significant increases in absorptive, and significant decreases in secretory transport in both jejunal and ileal sections.

The effect of pretreatment of male Sprague-Dawley rats with erythromycin or ketoconazole on the *in situ* gastrointestinal absorption of fexofenadine hydrochloride was investigated, as were the effects of co-administration of erythromycin, ketoconazole or verapamil (a P-glycoprotein inhibitor). In the pretreatment study, rats (4 males/group) were given oral doses of either erythromycin (7 mg/kg at 8, 16 and 24h prior to surgery), or ketoconazole (5 mg/kg at 24 and 48h prior to surgery). A third, control group, received no pretreatment. The isolated jejunal segments were then perfused with fexofenadine hydrochloride. Absorption of fexofenadine was increased by pretreatment (1.5-fold and 2.8-fold for erythromycin and ketoconazole, respectively).

In the co-administration study (4 males/group), the isolated segments were perfused with ketoconazole (1.5 mg/ml), erythromycin (2.1 mg/ml) or verapamil (0.1 mg/ml) for 5 minutes prior to co-administration with fexofenadine hydrochloride (0.2 mg/ml). A fourth, control group, received only the fexofenadine hydrochloride. Absorption of fexofenadine was increased by co-administration (3.4, 5.2 and 3.8-fold for erythromycin, ketoconazole and verapamil, respectively).

To summarise the above studies, pretreatment of dogs with ketoconazole or erythromycin increases the fexofenadine AUC following an iv dose of the latter. Systemic clearance appeared to be reduced mainly by a reduction in gastrointestinal clearance in the case of ketoconazole, but with erythromycin, the reduction was in biliary clearance. Furthermore, pretreatment of dogs with ketoconazole or erythromycin increases the AUC to a greater extent following an oral dose of fexofenadine.

Ketoconazole, erythromycin and verapamil significantly decreased the permeation of fexofenadine in the secretory direction through rat ileum *in vitro*. Only ketoconazole had a significant effect on transport of fexofenadine (an increase) in the absorptive direction in this model. In an *in situ* gastrointestinal absorption experiment in rats, pretreatment with ketoconazole or erythromycin increased the absorption of fexofenadine across the jejunal section. Co-administration of each of these compounds with fexofenadine was even more effective at increasing absorption of the latter in this model. The effect of verapamil on the absorption of fexofenadine suggests that P-glycoprotein might be responsible for the efflux portion of the cellular transport of fexofenadine, as verapamil is a known inhibitor of P-glycoprotein.

Toxicokinetics in dogs

The toxicokinetics from a 6 month dog study were reported. Beagle dogs (5/sex/group) were given oral doses of 0, 100, 300, or 900 mg/kg/day (by gavage, in 0.5% aqueous methylcellulose vehicle, as twice daily doses of 50, 150 or 450 mg/kg). Blood samples were collected at 1, 2, 4, 7 and 12h after the morning dose on days 1, 30 and 183 for analysis of fexofenadine levels. Samples from the high dose group on day 183 were also analysed for MDL 46,619, the methyl ester of fexofenadine which has been found in human faeces.
Mean group plasma concentrations of fexofenadine (C_{max} and C_{min}), and $AUC_{(0-12)}$ are tabulated in Appendix 3, page III 27. AUC increases with, though not in proportion to, dose. In the mid- and high-dose groups, AUC is greater at the end of the study, as is C_{min}, suggesting accumulation. (Previously, no accumulation was reported at the end of a one month study in dogs receiving up 300 mg/kg tid.)

During the course of the study, peak plasma concentrations in the high dose group ranged from 14,700 to 77,100 ng/ml. In comparison, peak plasma concentrations in man after a 180 mg tablet were less than 500 ng/ml.

Pharmacokinetic parameters in man and dog following an oral dose of fexofenadine

		Dose	**C_{max} (ng/ml)**	**AUC (ng.h/ml)**
			C_{max} (%CV)	*$AUC_{(0-\infty)}$ (%CV)*
Man*		180 mg tablet	494.24 (55.24)	3330.08 (39.49)
			C_{max} ± (SD)§	*$AUC_{(0-12)}$ ± (SD)§*
Dog	M	50 mg/kg bid	17,400 (8,100)	58,600 (27,600)
	F		16,200 (13,700)	55,500 (29,300)
	M	150 mg/kg bid	17,000 (2,800)	61,200 (11,600)
	F		22,400 (16,500)	92,600 (72,600)
	M	450 mg/kg bid	20,900 (4,100)	96,400 (22,400)
	F		28,200 (8,700)	106,000 (60,000)

* Data from bioequivalence study
§ Values are from day 1 of the 6 month toxicity study

Levels of the methyl ester, MDL 46,619, were below the limit of quantitation (0.5 ng/ml) in all samples measured (day 183 samples from the high dose animals).

The AUC's following the initial dose in the dogs in the low dose group are at least 16 times greater than in man after a 180 mg tablet, and therefore there is a good safety margin. Exposure of the dogs is more than adequate to cover the increase in dose in man.

TOXICOLOGY

Single dose toxicity

No additional single dose studies have been carried out. The statement concerning single dose studies in section 5.3 of the SPC is not relevant, and should be removed.

Repeated dose toxicity (Appendix 4)

A 6 month study in beagle dogs was carried out by the applicant in 1994-5, in compliance with GLP. Dogs (5/sex/group) received oral doses of 0, 100, 300, or 900 mg/kg/day (by gavage, in 0.5% aqueous methylcellulose vehicle, as twice daily doses of 50, 150 or 450 mg/kg); 3/sex/group were sacrificed at the end of the study, and 2/sex/group following a 4 week recovery period. Parameters examined were physical signs, ECG, ophthalmology, bodyweight, food consumption, haematology, clinical chemistry, urinalysis, organ weights, gross pathology and histopathology. In addition blood samples were taken during days 1, 30 and 183, for pharmacokinetic analysis.

Treatment-related effects were post-dose vomiting (infrequently in the low dose group), and white/yellow faeces (attributed to unabsorbed test article). No other toxicological signs were noted in any of the other parameters measured.

REPRODUCTIVE TOXICOLOGY

No additional reproductive toxicology studies have been carried out. Section 4.6 of the SPC, based on the results of reproductive studies with terfenadine and supporting pharmacokinetic studies submitted with the original application for fexofenadine hydrochloride, remains unchanged.

MUTAGENICITY

No additional mutagenicity studies were provided with this application. Those submitted with the original application for fexofenadine hydrochloride were negative.

CARCINOGENICITY

Carcinogenicity studies with fexofenadine have not been carried out. At the time of the original submission for fexofenadine hydrochloride, the applicant submitted carcinogenicity studies on terfenadine, contending that the exposure of mice and rats to the metabolite fexofenadine during the course of these studies provided sufficient evidence of a lack of carcinogenic potential of fexofenadine. This was acceptable to the Committee.

CONCLUSIONS

Preclinical studies to elucidate the mechanism of interaction of ketoconazole and of erythromycin with fexofenadine show that they increase the bioavailability of fexofenadine by increasing absorption, and reducing systemic clearance, although in slightly different ways; ketoconazole decreases gastrointestinal secretion, and erythromycin reduces biliary clearance.

In a 6 month oral toxicity study in dogs exposed to more than 16 times the AUC measured in man following a 180 mg dose, the only treatment-related effects were post-dose vomiting and white/yellow faeces.

Section 5.3 of the SPC should be amended to reflect the data more accurately. The first sentence should state the dose as '450 mg/kg administered twice daily'. The second sentence should be removed.

There are no objections on toxicological grounds to the grant of a Marketing Authorisation for this product, provided that the SPC is amended to the satisfaction of the Secretariat.

[redacted]
11 September 1996

Redacted under Section 40 of the FOI Act

Recommendation:

Summary of Product Characteristics
Section 5.3 should be amended to reflect the data more accurately. The first sentence should state the dose as '450 mg/kg administered twice daily'. The second sentence should be removed.

PART IV. MEDICAL ASSESSMENT

1. CLINICAL INDICATIONS

The new indications are proposed as follows:

'Telfast 120 is indicated for the relief of symptoms associated with seasonal allergic rhinitis.'

'Telfast 180 is indicated for the relief of symptoms associated with urticaria.'

2. DOSE AND DOSAGE SCHEDULES

Once daily dosing for adults and children over 12 years is proposed for both the new formulations. In all other respects the dosage instructions are the same as those already approved, stating that efficacy and safety have not been studied in children under 12, and that studies in the elderly and in those with renal or hepatic impairment indicate that dosage adjustments are not necessary in these groups.

3. CLINICAL PHARMACOLOGY

3.1 PHARMACODYNAMICS

3.1.1 Primary Pharmacodynamics

3.1.1.1 Histamine skin wheal and flare

The original submission included three studies in healthy volunteers investigating the inhibition of wheal and flare responses to fexofenadine hydrochloride. One of these (PJPR0002) investigated the effect of single dose oral administration at doses of 10, 20 ,40 80, 130, 200, 280, 360, 480, 640 and 800 mg and found no effect for the 10 mg dose, a dose response relationship between 20 mg and 130 mg, and no further increase in effect for the higher doses. The response to doses of 130 mg and higher lasted for more than 24 hours.

3.1.1.2 Symptoms induced by ragweed pollen

The original submission included a double-blind placebo-controlled study (PJPR0017) in patients with a history of seasonal allergic rhinitis who after prior sensitisation had symptoms induced by rag weed pollen. Fexofenadine hydrochloride at single doses of 60 mg and 120 mg gave symptom relief after 60 minutes, with maximum effect reached 2 hours and still maintained at the last observation at 5 hours.

3.1.2 Secondary Pharmacodynamics

3.1.2.1 Effects on Central Nervous System

A new study is submitted in which driving and psychomotor performance were assessed in healthy volunteers in which fexofenadine or placebo or active control was administered over 5 days in a six way cross-over study. On the fifth day of treatment alcohol was combined with study medication.

The primary performance parameter was Standard Deviation of Lateral Position, as measured during a 60 min 90 km driving test, the volunteer being instructed to drive as straight as possible in the middle of the carriageway. Overall deviation increased with time/distance travelled, and was greater on the fifth day when study medication was combined with alcohol which was dosed to give a blood concentration of just under 50 mg/dl, the legal limit for the country in which the trial was performed, the Netherlands. The results were as follows:

Standard Deviation of Lateral Position (cm)

Study Medication		Day 1		Day 4		Day 5	
		Mean	SE	Mean	SE	Mean	SE
Placebo		21.23	1.09	21.92	1.17	25.52	1.49
Fexofenadine	60 mg x2/d	21.68	1.07	21.24	1.08	24.27	1.38
	120 mg x1/d	21.63	0.99	21.94	1.11	24.08	1.26
	120 mg x2/d	20.33	0.96	20.53	0.96	23.15	1.07
	240 mg x1/d	20.99	0.94	21.45	1.02	23.39	1.30
Clemastine	2 mg x2/d	23.17	1.12	23.45	1.24	26.72	1.37

The active control clemastine significantly impaired performance, assessed by maintenance of lateral position, compared to placebo on Day 1 and Day 4. On Day 1 there was no significant difference between placebo and any of the fexofenadine groups, and on Day 4 one of the fexofenadine groups, 120 mg x2/d, showed close to significant improvement compared to placebo,

while the others showed no significant difference. In combination with alcohol fexofenadine 120 mg x2/d and 240 mg x1/d showed less impairment than placebo, while the other fexofenadine groups showed no difference from placebo.

Standard deviation of speed, a secondary performance parameter, gave the following results:

Standard Deviation of Speed (km/h)

Study Medication		Day 1		Day 4		Day 5	
		Mean	SE	Mean	SE	Mean	SE
Placebo		1.80	0.06	1.79	0.07	1.74	0.09
Fexofenadine	60 mg x2/d	1.95	0.10	1.77	0.08	2.02	0.10
	120 mg x1/d	1.97	0.12	1.75	0.09	1.85	0.11
	120 mg x2/d	1.86	0.08	1.66	0.06	1.82	0.09
	240 mg x1/d	1.88	0.09	1.73	0.09	1.92	0.09
Clemastine	2 mg x2/d	1.90	0.07	1.84	0.09	2.03	0.10

No significant differences were seen on Days 1 or 4, but on Day 5 in combination with alcohol clemastine, fexofenadine 60 mg x2/d and 240 mg x1/d gave significantly more impairment than alcohol alone.

The study included other psychomotor tests. Critical Flicker/fusion Frequency, the threshold in light frequency for perception of flicker, showed no significant effects of any regime or of alcohol. Critical Instability Tracking, the threshold of frequency of cursor deviations at which correction control is lost, showed significant impairment on Day 1 only by clemastine, fexofenadine 120 mg x1/d and 240 mg x1/d and impairment with alcohol in all groups, which with clemastine and fexofenadine 240 mg x1/d was significantly greater than for alcohol alone. Response speed in the Choice Reaction Time Test and correct detection in the Vigilance Test showed no significant effects on Day 1 or Day 4, and were reduced by alcohol, with significant additional reductions only with clemastine.

Comment:

Apart from relatively small effects seen for Standard Deviation of Speed and Critical Instability Tracking, this comprehensive testing of fexofenadine shows no general tendency towards impairment of driving performance or other psychomotor test. However, given the statement in the discussion of the study report that driving tests had to be stopped because of potentially dangerous driving for all treatments with the exception of fexofenadine 120 mg x2/d, the statement in the Summary of Product Characteristics requiring assessment of individual response prior to driving or operating machinery remains important.

3.1.2.1 Effects on the Heart

In view of the serious rhythm disorders now known to be associated with terfenadine, including QT prolongation, torsades de pointes, ventricular tachycardia, ventricular fibrillation, and cardiac arrest, the initial application for approval of fexofenadine included extensive data and discussion evaluating any possible influence of the compound on the electrocardiogram, particularly on the QT interval. No statistically significant changes were seen.

These findings are supported by new data in the present submission. A 70-day interim report on a 12 month double blind safety study in healthy volunteers of 240 mg fexofenadine daily compared

with placebo reports no statistically significant effects on QT_c QT, QRS, PR or heart rate; the values (msec) for QT_c are as follows:

Treatment (N)	Baseline Mean (SE)	Last visit Mean (SE)
Placebo (172)	397.7 (1.62)	400.1 (1.72)
Fexofenadine 240 mg x1/d (176)	399.1 (1.61)	397.5 (1.60)

The submission also includes a final report on a 6 month double blind safety study in healthy volunteers of 60 mg fexofenadine twice daily compared with placebo. In this study also there were no statistically significant effects on QT_c QT, QRS, PR or heart rate; the values (msec) for QT_c were as follows:

Treatment (N)	Baseline Mean (SE)	Last visit Mean (SE)
Placebo (209)	400.6 (1.50)	400.9 (1.42)
Fexofenadine 60 mg x2/d (216)	402.1 (1.46)	403.0 (1.40)

Outliers for QT_c were defined as patients in whom the interval was greater than 440 msec or increased by more than 10 msec. Numbers of outliers in these two studies were as follows:

Treatment	240 mg x1/d 70 days	60 mg x2/d 6 months
Placebo	8/172 (4.7%)	18/209 (8.6%)
Fexofenadine	4/176 (2.3%)	16/216 (7.4%)

Comment:

The additional data provided in the present data is reassuring as regards lack of effect of fexofenadine on cardiac rhythm.

3.1 PHARMACOKINETICS

The pharmacokinetics of fexofenadine were extensively studied for the previous submission and showed rapid absorption, negligible biotransformation, and excretion in the faeces (80%) and urine (11%).

3.3 SPECIAL GROUPS

No studies in special groups are presented with this application.

3.4 BIOAVAILABILITY

From the previous studies absolute bioavailability is estimated to be at least 33%.

3.5 BIOEQUIVALENCE

In the clinical safety and efficacy trials for seasonal allergic rhinitis and urticaria a 60 mg capsule was used. For marketing lactose-free tablet formulations of 120 and 180 mg strength have been developed. A bioequivalence study comparing the single 180 mg tablet with three 60 mg capsules gave the following results (adjusted means and pairwise comparisons are based on statistical analysis of natural-log transformed data):

	Treatment	Mean	%CV	Adjusted Mean	Ratio	90% CI
$AUC_{(0-\infty)}$	Tablet	3330.08	39.49	3091.31	95.17	86.0-105.3
(ng.h/mL)	Capsules	3396.65	32.60	3248.20		
t_{max}	Tablet	2.0	34.15	1.8	76.17	67.1-86.4
(h)	Capsules	2.6	38.77	2.3		
C_{max}	Tablet	494.24	55.24	444.75	100.02	87.3-114.6
(ng/mL)	Capsules	476.32	40.98	443.66		
$t_{½}$	Tablet	11.60	24.36	11.32	105.98	87.3-114.6
(h)	Capsules	10.93	23.39	10.68		
	Tablet	56.54	40.73	52.21	100.94	92.6-110.0
(L/h)	Capsules	54.37	31.49	51.72		

The 90% confidence intervals for the tablet formulation relative to the capsules for $AUC_{(0-\infty)}$, C_{max}, $t_{½}$ and Cl_{po} fall within the 80-125% range.

4. CLINICAL EFFICACY

4.1 CONTROLLED STUDIES

4.1.1 **A double-blind randomized placebo-controlled parallel study comparing the efficacy and safety of two dose strengths of fexofenadine HCl (120 & 180 mg once a day) vs cetirizine (10 mg once a day) in the treatment of seasonal allergic rhinitis (SAR). PJPR0032.**

In this multinational study conducted in 49 sites, 842 patients with seasonal allergic rhinitis who completed a 3-5 day placebo run-in period were randomized to two weeks treatment in one of the four treatment groups. Randomization was stratified according to severity of symptoms, and was performed by assignment of a sequential number associated with two unit dose blister cards, one for each week. 3 patients withdrew before taking study medication, leaving 839 patients, of whom 722 completed the study, who were included in the safety analysis. 18 patients had no baseline symptom assessment or no subsequent symptom assessment and were excluded from the efficacy analysis. The remaining 821 patients were included in an intent-to-treat efficacy analysis.

Study medication was taken each morning and symptoms were assessed by the patient at 12 and 24 hours after each daily dose. The symptoms assessed were:

- nasal congestion
- sneezing
- rhinorrhea
- itchy nose, palate, and/or throat
- itchy, watery, or red eyes

and they were assessed to give a total symptom score (TSS) according to the following scale:

0	Absent	Symptom not present
1	Mild	Symptom is present but is not annoying or troublesome
2	Moderate	Symptom is frequently troublesome, but does not interfere with either normal daily activity or sleep.
3	Severe	Symptom is sufficiently troublesome to interfere with normal daily activity or sleep
4	Very severe	Symptom is so severe as to warrant an immediate visit to the physician

Of the patients included in the efficacy analysis 420 were male and 401 female. Their ages ranged from 12-66.

The primary assessment of efficacy was the change from baseline of the 24 hour TSS, calculated by subtracting the average 24 hour score during the placebo run in period from the average 24 hour score during the study medication period. Means and standard errors for change from baseline are presented from an ANCOVA model containing site, treatment and baseline. The results obtained were as follows:

	Placebo	Fexofenadine HCl 120 mg	Fexofenadine HCl 180mg	Cetrizine 10 mg
N	201	211	202	207
Baseline Mean	7.3	7.2	7.4	7.3
SE	0.1	0.1	0.1	0.1
On medication Mean	5.8	4.7	4.5	4.4
SE	0.2	0.2	0.2	0.2
Change from baseline	-1.9	-3.0	-3.3	-3.3
SE	0.2	0.2	0.2	0.2
Versus placebo		-1.1	-1.4	-1.4
SE		0.2	0.2	0.2
P-value		0.0001	0.001	0.001
Versus fexofenadine 120 mg			-0.3	-0.3
SE			0.2	0.2
P-value			0.1339	0.1370
Versus fexofenadine 180mg				0.0
SE				0.2
P-value				0.9831

For the individual components of TSS changes from baseline were as follows (P-values for comparison versus placebo):

	Placebo	Fexofenadine HCl 120 mg	Fexofenadine HCl 180mg	Cetrizine 10 mg
N	201	211	202	207
Nasal congestion	-0.3	-0.4	-0.4	-0.4
SE	0.0	0.0	0.0	0.0
P-value		0.0052	0.0076	0.0199
Sneezing	-0.5	-0.7	-0.8	-0.8
SE	0.0	0.0	0.0	0.0
P-value		0.0001	0.0001	0.001
Rhinorrhoea	-0.5	-0.7	-0.8	-0.8
SE	0.0	0.0	0.0	0.0
P-value		0.0421	0.4484	0.0015
Itchy nose, palate or throat	-0.5	-0.8	-0.9	-0.8
SE	0.1	0.0	0.0	0.0
P-value		0.0001	0.0001	0.0001
Itchy, watery or red eyes	-0.4	-0.7	-0.8	-0.8
SE	0.0	0.0	0.0	0.0
P-value		0.0001	0.0001	0.0001

A protocol correct analysis restricted to 765 patients with no major protocol variations showed essentially similar findings for TSS comparisons.

Secondary end-points included changes with respect to baseline for:

- average pre-dose previous 12 h TSS
- average 12 h post dose previous 12 h TSS
- average pre-dose previous 30 min TSS
- TSS improvement from baseline in 24 hour
- patient assessment of overall effectiveness
- physician assessment of overall effectiveness
- change in average somnolence

Statistically significant improvement over placebo was seen for the first six of these end-points for all active treatment groups. The comparison for change in average somnolence suggested that cetrizine caused more somnolence than placebo and fexofenadine, but this was not confirmed in the analysis using the model including treatment by centre interaction.

Comment:
The trial report is noteworthy for the exceptionally clear presentation of the trial methodology and results. It is of interest that it was finalised on 20 May 1966, the trial having been conducted between May 1995 and January 1996, and the finalised database having been unblinded on 21st March 1996. The trial provides convincing evidence of relief of the symptoms of seasonal allergic rhinitis by a single dose of fexofenadine 120 mg or 180 mg.

4.1.2 **A multi-centre double-blind randomised placebo controlled parallel group study comparing the efficacy and safety of four dosage regimes of fexofenadine hydrochloride in the treatment of chronic idiopathic urticaria. PJPR0019**

In this multinational study conducted in 52 sites 224 patients with chronic idiopathic urticaria who completed a 3-5 day placebo run-in period were randomized to two weeks treatment in one of the four treatment groups. Randomization was performed by assignment of a sequential number associated with a set of weekly unit dose blister cards, one card for each week. 2 patients withdrew before taking study medication, leaving 222 patients who were included in the safety analysis. 14 patients had no baseline symptom assessment or no subsequent symptom assessment and were excluded from the efficacy analysis. The remaining 208 patients were included in an intent to treat efficacy analysis. Of these 88 were male and 120 female; their ages ranged from 18 to 83 years.

Study medication consisting of 4 capsules was to be taken one hour before food at intervals of 24 hours for 6 weeks.

On the basis of initial power calculations 300 protocol correct patients were required and the intention was to recruit 350 patients. However during the study a power recalculation was performed on the basis of blinded baseline data from 75-100 patients. As this indicated that 200 protocol correct patients would suffice, the trial was halted early.

Comment:

This change of size of the trial was unprotocolled and is a *prima facie* cause for concern. However, if the second power calculation was indeed performed on blinded baseline data, and blinded on-treatment data were not examined, this should not affect the validity of the trial. The description of the unblinding of the drug code, which was performed on 15 April 1996, the last patient having completed on 8 March 1996, suggests that blinded grouped on-treatment data could not have been examined The attention of the statistical assessor is drawn to this irregularity.

Study medication was taken each morning and symptoms were assessed by the patient each day. The symptoms assessed for the primary end-point, mean daily total symptom score, were pruritus and wheals, scored as follows:

Pruritus score

0	None	No itching present
1	Mild	Minor irritation; hardly noticeable; not annoying or troublesome
2	Moderate	Annoying and troublesome; may somewhat interfere with either normal daily activity or sleep.
3	Severe	Very annoying and troublesome; substantially interferes with normal daily activity or sleep

Number of wheals score

0 None
1 1-5
2 6-15
3 16-25
4 >25

Means, standard errors and p-values for change from baseline are presented from an ANCOVA model containing site, treatment and baseline from which data from one outlying patient has been excluded.

Comment:

The justification for excluding this patient was that the mean baseline TSS was 2 but the on medication TSS was 7 (including one value before starting medication) for the 5 days before the patient's withdrawal for an adverse event, patient's request and non-compliance. The differences between the 180 mg and 240 mg groups and placebo remain statistically significant if this patient's results are included: as the primary analysis is protocolled to be intent-to-treat, the exclusion of this patient unnecessarily complicates the presentation of the results.

Results for the primary analysis were as follows:

	Placebo	Fexofenadine HCl 60 mg	Fexofenadine HCl 120mg	Fexofenadine HCl 180 mg	Fexofenadine HCl 240mg
N	46	40	36	47	39
Baseline raw mean	3.80	3.93	4.32	3.91	4.08
SE	0.28	0.31	0.26	0.22	0.30
On medication raw mean	3.45	3.06	3.17	2.40	2.70
SE	0.28	0.27	0.29	0.25	0.30
On medication adjusted mean	3.68	3.15	3.06	2.62	2.72
SE	0.23	0.24	0.25	0.22	0.24
Versus placebo		-0.53	-0.62	-1.06	-0.96
SE		0.32	0.34	0.31	0.33
P-value		0.1005	0.6760	0.0008	0.0041
Versus fexofenadine 60 mg			-0.09	-0.53	-0.42
SE			0.35	0.32	0.34
P-value			0.8001	0.1046	0.2122
Versus fexofenadine 120 mg				-0.44	-0.34
SE				0.33	0.35
P-value				0.1839	0.3319
Versus fexofenadine 180 mg					+0.10
SE					0.33
P-value					0.7486

For the pruritus score the following results were obtained:

	Placebo	Fexofenadine HCl 60 mg	Fexofenadine HCl 120mg	Fexofenadine HCl 180 mg	Fexofenadine HCl 240mg
N	46	40	36	47	39
Baseline raw mean	1.78	1.76	1.94	1.69	1.75
SE	0.11	0.14	0.12	0.09	0.13
On medication raw mean	1.61	1.28	1.32	0.98	1.02
SE	0.12	0.12	0.13	0.11	0.12
On medication adjusted mean	1.66	1.31	1.27	1.11	1.06
SE	0.10	0.11	0.12	0.10	0.11
Versus placebo		-0.36	-0.39	-0.56	-0.60
SE		0.15	0.15	0.14	0.15
P-value		0.0167	0.0120	0.0001	0.0001
Versus fexofenadine 60 mg			-0.03	-0.20	-0.25
SE			0.16	0.15	0.16
P-value			0.8351	0.1810	0.1152
Versus fexofenadine 120 mg				-0.17	-0.21
SE				0.15	0.16
P-value				0.2802	0.1823
Versus fexofenadine 180 mg					-0.05
SE					0.15
P-value					0.7604

All doses gave significantly greater improvement than placebo, with a significant test for linear trend (p=0.0001).

For the wheals score the following results were obtained:

	Placebo	Fexofenadine HCl 60 mg	Fexofenadine HCl 120mg	Fexofenadine HCl 180 mg	Fexofenadine HCl 240mg
N	46	40	36	47	39
Baseline raw mean	2.02	2.17	2.38	2.23	2.33
SE	0.18	.0.19	0.17	0.14	0.22
On medication raw mean	1.84	1.78	1.85	1.42	1.68
SE	0.17	0.18	0.19	0.16	0.21
On medication adjusted mean	2.03	1.84	1.79	1.50	1.65
SE	0.14	0.15	0.15	0.14	0.15
Versus placebo		-0.18	-0.24	-0.52	-0.37
SE		0.20	0.20	0.19	0.20
P-value		0.3467	0.2445	0.0064	0.0629
Versus fexofenadine 60 mg			-0.05	-0.34	-0.19
SE			0.21	0.20	0.21
P-value			0.7973	0.0884	0.3573
Versus fexofenadine 120 mg				-0.28	-0.14
SE				0.20	0.21
P-value				0.1644	0.1577
Versus fexofenadine 180 mg					+0.15
SE					0.20
P-value					0.4591

For the wheals score only the 180 mg group gave a reduction which differed significantly from that seen with placebo. There was a statistically significant test for linear trend ($p = 0.0159$).

In addition to the results for the primary end-point, all dose levels of fexofenadine differed significantly from placebo in reducing the interference of the skin condition with sleep, and with daily activity. For the patient's assessment of overall effectiveness, there was a statistically significant active versus placebo comparison ($p = 0.0084$) but only the 60 mg and 180 mg groups showed statistically significant advantage over placebo ($p = 0.0157, 0.0119$).

For the physician's assessments the number of lesions, the intensity of erythema, the extent of skin area, and the size of the lesions at the end of the study showed no statistically significant advantage of active versus placebo. Statistically significant advantages of active versus placebo were seen for overall severity of skin condition during the last two weeks, overall severity of skin condition at end of study, degree of symptom control, and overall effectiveness of study medication all showed statistically significant advantage of active versus placebo.

Comment:
The trial report clearly presents the trial methodology and results. It is of interest that it was finalised on 29 May 1966, the trial having been conducted between March 1995 and March 1996, and the database having been unblinded on 15th April 1996. The trial provides convincing evidence of relief of the symptoms of urticaria by a single dose of fexofenadine 180 mg.

4.2 UNCONTROLLED STUDIES

No uncontrolled patient studies are reported.

4.3 SPECIAL GROUPS

Children aged 12-17 were included in the seasonal allergic rhinitis trial but not in the chronic idiopathic urticaria trial. The applicant argues that, as the incidence and type of adverse event was similar in the children to those seen in the older age group, the indication of urticaria could also be extended to children of this age group.

4.4 OVERALL ASSESSMENT OF EFFICACY

For seasonal allergic rhinitis, for which fexofenadine is already licensed, the new trial data provide convincing evidence that a single daily 120 mg dose is effective.

For chronic idiopathic urticaria the evidence is also convincing for the effectiveness of a single daily 180 mg dose. However the applicant requests the wider indication of urticaria. The parent compound, terfenadine is not specifically licensed for urticaria, although it has a broad indication for 'allergic skin conditions'. Given that there is no trial data with fenoxfenadine on types of urticaria other than chronic idiopathic urticaria, and that an appropriate dosing regime cannot be recommended, the indication should be limited to this specific type.

5. CLINICAL SAFETY

5.1 SUMMARY OF ADVERSE REACTIONS - VOLUNTEERS

No adverse events were reported in the three clinical pharmacology studies, not included in the original application, which are included in this application.

The long term placebo-controlled safety study of daily 240mg fexofenadine in healthy volunteers is still ongoing. Safety data from 225 volunteers followed for a median of 6.5 months shows no difference between active and placebo groups in the incidence or nature of adverse events, the commonest in both groups being headache, viral infection and upper respiratory tract infection.

5.2 SUMMARY OF ADVERSE REACTIONS - PATIENTS

5.2.1 **A double-blind randomized placebo-controlled parallel study comparing the efficacy and safety of two dose strengths of fexofenadine HCl (120 & 180 mg once a day) vs cetirizine (10 mg once a day) in the treatment of seasonal allergic rhinitis (SAR). PJPR0032.**

No deaths occurred during this trial. Serious treatment emergent adverse events were limited to one case of deafness in a patient receiving fexofenadine 120 mg and one case of acute appendicitis in a patient receiving fexofenadine 180 mg. Incidences of adverse events, both treatment related and treatment unrelated, were similar between the groups. No new safety hazard was identified.

5.2.2 **A multi-centre double-blind randomised placebo controlled parallel group study comparing the efficacy and safety of four dosage regimes of fexofenadine hydrochloride in the treatment of chronic idiopathic urticaria. PJPR0019**

No deaths occurred during this trial. Serious treatment emergent adverse events were limited to one case of facial angioedema and one case of uterine enlargement (fibromyoma), both in the placebo group. Incidences of adverse events, both treatment related and treatment unrelated, were similar between the groups. No new safety hazard was identified.

5.3 OVERALL COMMENT ON SAFETY

The new data presented in this application are reassuring in terms of the known safety profile of fexofenadine.

6. EXPERT REPORT

The Clinical Expert is [redacted] formerly [redacted]. The report provides a clear presentation of the data and justification for the new formulations, dosing regime and indication.

7. PATIENT INFORMATION LEAFLET

The Patient Information Leaflets are appropriately worded. A minor change will be required to the wording if the indication for the 180 mg tablet is restricted to chronic idiopathic urticaria.

8. LABELLING

The labelling is appropriate.

9. APPLICATION FORM (MLA 201)

No comments.

10. SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

Apart form the new doses and indication there is no change in the Summary of Product Characteristics.

11. DISCUSSION

The clinical data presented in this application provide an adequate justification for the new formulations and dose regime. The only outstanding issue in the view of the assessor is whether the trial data for chronic idiopathic urticaria can be extrapolated to other forms of urticaria.

13. RECOMMENDATION

The Committee may consider that the application should be approved, subject to the restriction of the new indication to 'chronic idiopathic urticaria'.

Sign: Pharm, Tox, Med.

MAIN COMMITTEE	**DRAFT ADVICE**
DATE OF MEETING:	**9 October 1996**
M.A. No.:	**04425/0157-0158**
COMPANY:	**Marion Merrell Ltd**
PRODUCT:	**Telfast tablets 120 mg and 180 mg**
ACTIVE CONSTITUENT:	**Fexofenadine**
THERAPEUTIC CLASS:	**H1-histamine antagonist**
KEY WORDS:	

On the evidence before them, the Committee/Sub Committee advised the grant of a Marketing Authorisation(s) provided the applicant complies with the following condition(s):

1. The indication for Telfast 180 mg should be restricted to relief of symptoms associated with chronic idiopathic urticaria.

2. Section 5.3 of the SPC should be amended to the satisfaction of the Secretariat to reflect the data more accurately. The first sentence should state the dose as '450 mg/kg administered twice daily'. The second sentence should be removed.

[redacted]

Redacted under sections 41 and 43 of the FOI Act