NIHS Notification no. 2711

24th July 2000

To Director-General of Safety Division, MHW

Director of National Institute of Health Sciences

Evaluation Report

The Pharmaceutical and Medical Devices Evaluation Center has evaluated a drug approval application and the result is given in this report.

[Product Name]	Allegra Tablets 60 mg
[Generic Name]	Fexofenadine hydrochloride
[Applicant]	Aventis Pharma Ltd. (At the time of application, Hoechst Marion Roussel Ltd.)
[Date of Submission]	29th July 1999
[Formulation and Content]	Tablets containing 60 mg/tablet of fexofenadine hydrochloride
[Application Classification]	Drug for Medical Use (1) (Drug Containing a New Active Ingredient)
[Chemical Structure]	As attached
[Evaluated by]	Evaluation Division II

Attached

Chemical Structure, Omitted

Chemical name: (±)-2-{4-[1-hydroxy-4-[4-(hydroxydiphenylmethyl) piperidino]butyl]phenyl}-2-methylpropanoic acid monohydrochloride

Result of Evaluation

24th July 2000

[Product Name]	Allegra Tablets 60 mg
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[Applicant]	Aventis Pharma Ltd. (At the time of application, Hoechst Marion Roussel Ltd.)
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[Results of Evaluation]

The Pharmaceuticals and Medical Devices Evaluation Center (hereinafter referred as "the Evaluation Centre") has concluded that efficacy and safety of Allegra Tablets 60 mg with the indications of allergic rhinitis and urticaria, was verified based on the submitted data. Results from Japanese dose selection studies and results from overseas' clinical studies, which were considered to be extrapolatable based on the Japanese dose selection study results, have shown efficacy and safety for both indications. With regard to safety of Allegra Tablets, particularly safety on the circulation system, findings or adverse drug reactions from non-clinical and clinical study results did not cause specific concerns and there were no other significant adverse drug reactions, etc. However, as data on the long-term use or use in the geriatric population were insufficient, therefore, appropriate post marketing surveillance may be required.

As a consequence of the above, we have no objection in granting approval with the following indications and dosage and administration method.

[Indications]
Allergic rhinitis, urticaria

[Dosage and Administration Method]

Usually for adults, orally administer 60mg of fexofenadine hydrochloride twice daily.

The dose should be adjusted according to the symptoms.

Evaluation Report (1)

29th June 2000

1. OUTLINE OF THE PRODUCT

[Product Name]	Allegra Tablets 60 mg
[Generic Name]	Fexofenadine hydrochloride
[Applicant]	Aventis Pharma Ltd. (At the time of application, Hoechst Marion Roussel Ltd.)
[Date of Submission]	29th July 1999
[Formulation and Content]	Tablets containing 60 mg/tablet of fexofenadine hydrochloride
[Filed Indications]	Allergic rhinitis, urticaria
[Filed Dosage and Administration Method]	Usually for adults, orally administer 60mg of fexofenadine hydrochloride twice daily. The dose should be adjusted according to the symptoms.

2. OUTLINE OF SUBMITTED DATA AND SUMMARY OF EVALUATION

A. Data on Origin or Details of Discovery and Use in Overseas Countries, etc.

Fexofenadine hydrochloride is an active metabolite of terfenadine, which has been developed by Marion Merel Dow in the US (current Aventis Pharma). Allegra Tablets have been approved in 85 countries including the US and the EU countries as of June 2000. In the US and the EU countries, the approved indications are “seasonal allergic rhinitis and chronic urticaria”. In Japan, Hoechst Marion Roussel (current Aventis Pharma) has developed Allegra Tablets and applied for import approval with indications for “allergic rhinitis and urticaria”.

Terfenadine is the parent compound of fexofenadine. The main action of terfenadine is anti-histaminic with a low incidence of central nervous system (CNS) depressive adverse drug reactions (e.g. somnolence). Terfenadine was approved in the West in 80s and was sold in more than 100 countries worldwide. However, reports of adverse events across the globe indicated serious cardiovascular adverse drug reactions associated with QT interval prolongation that was considered to be caused by the un-changed form when terfenadine was used in patients with hepatic impairment or concurrently with a drug which inhibits metabolising enzymes of terfenadine. Fexofenadine has been developed as an agent that does not cause such adverse drug reactions. The applicant argues that Allegra Tablets have very weak CNS depressive actions and QT prolongation activities and it is safer than other similar drugs. In Japan, terfenadine has been approved on 23rd January 1990 with indications for "bronchial asthma, allergic rhinitis, urticaria, pruritus associated with skin disorders (eczema/dermatitis, pruritus cutaneous)", however, the "Precautions for Use", etc., were amended to call attention to an occurrence of such adverse drug reactions.

B. Data on Physical and Chemical Properties, Specifications, Test Methods, etc.

The structure of the drug substance, fexofenadine hydrochloride, was determined by elementary analysis, NMR, MS, etc. Polymorphism of the drug substance did not show xxx. The analysis with a chiral column suggested the compound was racemate. X analogs showed good separations under HPCL. Up to XX% of force-decomposed compounds are reported.

The Evaluation Centre inquired xxxxxxxx
xxxxxxx, and the applicant explained xxxxxx
xxxxxxxxxx. The Evaluation Centre also made inquiries on the Specifications and Test Methods. These instructions included "the melting point specification should clearly state that the melting point is the onset temperature and the range of the specification should be narrowed" and "the purity test specification should be not more than xx". The

applicant agreed to make the amendments. The applicant also agreed to amend the assay method xxx xxx following the query. The Evaluation Centre accepted their responses.

On the subject of the drug product, the Evaluation Centre questioned xxxxx such as the assay methods. The applicant made some amendments and the Evaluation Centre accepted the amendments.

C. Data on Stability

With regard to the stability, a long-term storage study, an accelerated study and a stress study with the drug substance were performed and the applicant reported that all of studies revealed no major concern and the drug substance was stable for three years at room temperature. The above studies were also performed with the drug product and it was reported to be stable. The Evaluation Centre accepted those explanations. The long-term storage study of drug product was still ongoing and data obtained in two years was presented. A tentative expiry date was set at two years. However, new data up to three years was submitted later. The data did not raise any concern and the applicant stated that they would not set an expiry date. The Evaluation Centre accepted this.

D. Data on Acute Toxicity, Subacute Toxicity, Chronic Toxicity, Teratogenicity and Other Toxicity

Toxicity studies carried out with fexofenadine were single dose toxicity studies, repeated dose toxicity studies, mutanogenicity studies and antigenecity studies.

The single dose toxicity studies were implemented in mice, rats and dogs and they received either oral or intravenous administration. The approximate lethal doses were estimated at not less than 5146mg/kg in mice with oral administration (Cmax of 5191.1ng/mL, $AUC_{0-\infty}$ of 30220ng·hr/mL, hereinafter expressed as plasma fexofenadine concentration), not less than 5146mg/kg in rats with oral administration (Cmax of

1353ng/mL for male or 1341ng/mL for female, AUC_{0-24} of 7179ng·hr/mL for male or 6931ng·hr/mL for female), not less than 450mg/kg n dogs with oral administration (Cmax of 58381ng/mL, AUC_{0-96} of 358457ng·hr/mL) and not less than 25mg/kg and not more than 50 mg/kg in rats with intravenous administration. It was estimated that AUC in mice, rats and dogs after oral administration was 8.0 times, 1.9 times (male)/1.8 times (female) and 94.3 times of the human daily exposure, respectively.

The repeated dose toxicity studies were implemented in mice, rats and dogs and fexofenadine was administered orally or as feed-mixed. When mice received one-month administration of fexofenadine mixed in feed, an accumulative weight gain of the group fed with feed containing 5.0% fexofenadine was lower than the group fed with feed containing 0.5% fexofenadine by 64% (male) and 90% (female). When rats were fed with feed containing fexofenadine for one month, there were no changes in general signs, bodyweights and feed consumptions in either the 0.5% feed-mix group or the 5.0% feed-mix group. A one-month oral study in dogs showed no toxicity findings that were considered to be effects of the drug even at 803mg/kg/day (the highest dose). The No Toxicity Dose was estimated at 803mg/kg/day and the daily exposure at that dose was 187.6 times (male) or 293.8 times (female) of the exposure to human. In a one-month oral dose (impurity) toxicity study in dogs, fexofenadine which contained xxx of impurities was used. The No Toxicity Dose was estimated at 900g/kg/day. A three-month feed-mix toxicity comparison study in mice for comparing toxicity profiles of terfenadine and fexofenadine showed no differences in toxicological findings of general signs, etc. Plasma fexofenadine concentrations of animals received terfenadine mixed in feed were higher than that of animals received fexofenadine mixed in feed. In a six-month dog study, vomiting and cream coloured faeces (including unabsorbed test material) were observed in all active drug groups, but there was no other abnormality. Therefore, the No Toxicity Dose was estimated at 900mg/kg/day and the daily exposure at the dose level was 121.6 times (male) or 129.5 times (female) of the exposure to human. For rat three-month oral and six-month mixed feed studies, results of studies with terfenadine were submitted.

For reproductive and developmental toxicity studies, results of studies with terfenadine were submitted. In organogenesis follow-up TK studies in rats and rabbits, the plasma fexofenadine concentrations of both dams and foetuses after fexofenadine administration were higher than the plasma fexofenadine concentrations after terfenadine administration. The daily fexofenadine exposures of rat dams and rabbit dams at Day 10 or Day 11 were estimated at 3.1 times and 26.7 times of the human exposure, respectively. In the rat fertility study, the organogenesis study (1) and the peri/postnatal study, it was not possible to clearly distinguish effects of terfenadine from effects of fexofenadine on dams, foetus and pups. Therefore, the Evaluation Centre concluded that fexofenadine should carry the same "Precautions for Use" in pregnant, parturient and lactating women as terfenadine.

The mutanogenecity studies carried out were; reverse mutation tests with bacteria, a gene mutation study with Chinese hamster ovary cells, a mice micronucleus study, a rat lymphoma chromosomal aberration study. All results were negative. Therefore, the possibility of fexofenadine to have a mutanogeneic potential *in vivo* was considered to be low.

Results of studies with terfenadine were submitted as carcianogenecity studies. To estimate plasma fexofenadine concentrations after fexofenadine administration in these studies, mouse and rat one-month mixed feed follow-up TK studies were implemented. The fexofenadine daily exposures after administration of fexofenadine were estimated at 3.0 times (male) or 1.5 times (female) in mice and 3.1 times (male) or 2.4 times (female) in rats of the human exposure.

No dependency study was carried out for reasons including lack of findings indicative of central actions in the repeated dose studies.

Antigenecity studies were implemented in mice and guinea-pigs. The antigenic potential of fexofenadine was considered to be low.

Issues on safety of impurities were believed to be absent.

E. Data on Pharmacological Action

(1) Studies Supporting Efficacy

1) Effects on animal disease models

In an antigen induced allergic rhinitis model in guinea-pigs, oral administration of 20mg/kg fexofenadine hydrochloride suppressed an increase in nasal resistance induced by the antigen.

Similar to terfenadine, fexofenadine (0.03 to 1mg/kg, i.v.) suppressed rat 48-hour allogeanic passive cutaneous anaphylaxis (PCA) in a dose dependent fashion.

Intravenous administration of 3mg/kg fexofenadine prolonged the survival time of active sensitised rats with the antigen induced generalised anaphylactic shock without affecting the death rate, similar to terfenadine.

Oral administration of 2 to 8.2mg/kg of fexofenadine suppressed an increase in the antigen induced airway resistance in active sensitised guinea-pigs in a dose dependent fashion. Terfenadine (8.4m/kg) also showed similar suppression.

In conclusion, the above has demonstrated that fexofenadine suppresses the symptoms of Type I allergic model animals as with terfenadine.

2) Pharmacological study on the mode of action

The K_i values for affinity of fexofenadine and terfenadine to histamine H_1 receptors in cerebrocortical membrane preparation of rats were 176nM and 313nM, respectively.

In isolated guinea-pig ileum preparation, fexofenadine (0.1, 0.3μM) shifted the histamine concentration-response curve in parallel to the right. The effect was sustained for 120

minutes after washing. Fexofenadine did not show effects on the constriction induced by ACh, Ba^{2+} and Ca^{2+}. In contrast, terfenadine suppressed the maximum response of histamine concentration-response curve. At 0.3μM or higher concentration, terfenadine suppressed the maximum response of ACh and Ba^{2+} induced constriction and shifted the concentration-response curve of Ca^{2+} in parallel to the right.

In isolated guinea-pig trachea preparation, between 10^{-7} and 3×10^{-6} M fexofenadine shifted the histamine concentration-response curve in parallel to the right and the pA_2 value was 7.52. Terfenadine shifted the histamine concentration-response curve in parallel to the right. Terfenadine at 3×10^{-6} M or higher concentration also curbed the maximum response.

In the hind-limb perfusion of anaesthetised dogs, intravenous administration of 0.03mg/kg fexofenadine suppressed a fall of the perfusion pressure resistance induced by histamine. At 0.3 and 3mg/kg, fexofenadine suppressed histamine induced reactions even after two hours from the administration. However, fexofenadine had no effect on an increase in the perfusion pressure caused by phenylepheine. Similarly, at 0.3 and 1mg/kg, terfenadine suppressed a fall of the perfusion pressure induced by histamine.

In guinea-pigs, oral fexofenadine administration (0.1 to 6 mg/kg) suppressed increases in histamine induced respiratory track resistance. The $Dose\text{-}Ratio_2$ value (a dose required to shift dose-response curve of histamine in parallel to the right by twofold) was 0.34 to 0.76mg/kg. The terfenadine's $Dose\text{-}Ratio_2$ value was 0.38mg/kg.

Oral fexofenadine administration (0.4 to 3.2 mg/kg) suppressed histamine induced wheals in guinea-pigs, dose dependently. The time-change of the suppression at 1.6mg/kg was similar to terfenadine (1.6mg/kg). The maximum suppression was observed at two hours after administration and then the inhibitory action was reduced gradually.

The above suggested that fexofenadine has a selective anti-histamic action.

Fexofenadine inhibited histamine release from peripheral basophil of healthy volunteers and peripheral leukocyte of atopic dermatitis patients induced by stimulation of antihuman IgE antibody. It also suppressed ECP production and LTC_4 release from peripheral eosinophil induced by A-23187 stimulation in healthy volunteers. However, the suppression of the migration of peripheral eosinophil and neutrophil induced by FMLP stimulation in healthy volunteers were weak and fexofenadine did not have effects on IL-4 production of peripheral eosinophil induced by antihuman IgE antibody stimulation in healthy volunteers.

In an antigen induced immediate asthmatic response model in active sensitised guinea-pigs, fexofenadine (8.2mg/kg, p.o.) suppressed an increase in the respiratory tract resistance. At the same time, it reduced the level of LT released in bronchoalveolar lavage fluid (BALF). However, it did not have an effect on the level of histamine.

Fexofenadine (10^{-9} to 10^{-3}M) suppressed production of IL-8 and GM-CSF and expression of sICAM-1 in the nasal mucosa epithelial cells isolated from seasonal allergic rhinitis patients, which had been cultivated with activated eosinophil. It also inhibited the migration of eoshinophil and their adhesion to vascular endothelium induced by supernatant of culture of the nasal mucosa epithelial cells.

The affinity to α_1, α_2, β adrenargic receptors, m_1, m_2, m_3, m_4, m_5 muscarinic receptors, 5-HT_{1A}, 5-HT_{2A} serotonine receptors, NK_1, NK_2 tachykinin receptors and type L Ca^{2+} channel was low.

The presented data suggested fexofenadine had inhibitory actions on the chemical mediator release, inflammatory cytokine production of the nasal mucosa epithelial cells and eosinophil migration, in addition to the selective H_1 receptor antagonistic action.

3) Pharmacological studies on optical isomer

K_i values of (±)-fexofenadine, (+)-fexofenadine and (-)-fexofenadine at H_1 receptors of cerebrocortex of the rat were 176, 170 and 152nM, respectively. The inhibitory actions

of (+)-fexofenadine and (-)-fexofenadine against histamine constriction in an isolated guinea-pig ileum preparation were almost the same. The (+)-fexofenadine and (-)-fexofenadine (0.4 to 3.2 mg/kg, p.o.) dose dependently suppressed histamine induced wheals and their effects were the same as the (±)-fexofenadine. As with (±)-fexofenadine, affinity of (+)-fexofenadine and (-)-fexofenadine to α_1, α_2, β receptors, m_1, m_2, m_3, m_4, m_5 receptors, 5-HT_{1A}, 5-HT_{2A} receptors and type L Ca^{2+} channel was low.

In conclusion, both optic isomers have anti-histamine effects and there were no big differences in their effects were.

(2) General pharmacology studies

Investigations on administration routes were carried out with intravenous and intraperitoneal administration, because in rats the absorption rate of oral administration, which was the clinical administration route, is only 30%, the AUC rate of radioactivity of oral administration vs intravenous administration was only 3.5% to 3.8 % and metabolism of fexofenadine *in vivo* was minimal.

When rats received intraperitoneal administration of 300mg/kg fexofenadine, whitening of ears, distress and hypothermia occurred. One out of four animals died at three hours from administration and one animal died on each of Day 2 and Day 3. When mice received intraperitoneal dosing of 30mg/kg fexofenadine, a decrease in the locomotor activity was observed. When 0.8% and 1.6% solutions were subcutaneously administered to guinea-pigs, it inhibited skin constrictions and led to hardening of the skin after 24 hours. When nullipara and pregnant rats received intravenous administration of 3mg/kg of fexofenadine, a mild increase in the uterine motility was observed. When rats received intraperitoneal administration of 10mg/kg of fexofenadine, gastric juice excretion was suppressed and increases in Na^+ and Cl^- excretions were observed at 30mg/kg. Although the administration routes used in the studies were different, all of those changes occurred when 5 to 15 times or more of the clinical dose was administered intraperitoneally. Those changes were considered clinically insignificant.

Electrophysiological investigation was carried out in patch cramp tests. In human myocardial delayed rectifier K^+ channel (fHK Kv1.5), which was expressed in human embryo kidney cultured cells (HEK-293), fexofenadine had no effect on the delayed rectifier K^+ current. A patch cramp test in human delayed rectification K^+ channel (HERG) and transient outward K^+ channel (Kv4.3), which were expressed in mouse cultured L cells, demonstrated weak suppressions of the HERG (I_{kr}) current and the Kv4.3 (I_{to}) current (IC_{50}: 30μM, 112μM) by fexofenadine. A patch cramp test was carried out in ventricular muscle cells isolated from mature guinea-pigs and rat offspring to investigate the effects on the membrane. Fexofenadine slightly suppressed the delayed rectification K^+ current at 10μM, but did not affect the Na^+ current and the Ca^{2+} current.

When 30mg/kg of fexofenadine was administered twice a day for five days to unanaesthetised unrestraint dogs, prolongation of the QTc interval was not observed. The plasma fexofenadine concentration (4,382.2ng/mL) was approximately 10 times of the plasma MDL 16,455 concentration (420.0ng/mL) when 3mg/kg of terfenadine was administered, which showed prolongation of the QTc interval. Also, it was approximately 14 times higher than Cmax (315ng/mL) of a repeated dose of fexofenadine (60mg, twice daily) in Japanese healthy adults.

In a fexofenadine 6-month repeated dose toxicity study in dogs, no ECG abnormalities were observed on Day 1, Day 31, Day 90 and Day 178. Plasma fexofenadine concentration on Day 183 (Cmax) was 48,800mg/mL in male and 50,200ng/mL in female, which were 155 and 159 times those of Cmax at the clinical dose, respectively. A one-month repeated dose study did not show ECG abnormality. The above results suggested fexofenadine was not involved in prolongations of the QT and QTc interval.

Effects on the heart were investigated by intravenously administering 3 and 10mg/kg of fexofenadine continuously for one hour to anaesthetised rabbits. Results showed no effects on the QT or QTc interval, heart rate and blood pressure. The plasma fexofenadine concentration was 9,777ng/mL at one hour from the start of the administration. When 1mg/kg of terfenadine was continuously administered in the vain,

the QT and QTc interval was prolonged and systolic pressure was reduced. The plasma fexonadine concentration was 83.5ng/ml. The plasma fexofenadine concentration after fexofenadine administration was 117 times higher than the above and was 31 times higher than Cmax at the clinical dose (315ng/mL). Furthermore, cumulative intravenous administration of fexofenadine (at 0.1, 0.2, 0.7, 2.0 and 7.0mg/kg), which was given under anaesthetic to maintain the heart rate at 325 bpm, did not affect the QT interval.

It has been reported that fexofenadine (100mg/kg, i.v.) has little effect on ECG in guinea-pig experimental models. It has also been reported 50mg/kg of i.v. fexofenadine does not prolong the QT interval in a guinea-pig experimental model, whereas 12.5mg/kg terfenadine intravenous administration significantly prolonged the QTc interval for 48msec at 15 minutes after administration.

Based on the above, it was suggested that fexofenadine was a very safe drug in term of pharmacological effects on the cardiovascular system.

The Evaluation Centre presented queries to the applicant on the following points.

The Evaluation Centre asked for explanation of the rational for the administration routes, the dosed amounts and duration of fexofenadine and terfenadine treatment used in the *in vivo* experimental systems. The applicant explained that they carried out experiments with intravenous administration because bioavailability of oral dose of fexofenadine in rats was low. Studies in dogs were also carried out with intravenous administration. They explained they used the dose amounts that showed a sufficient anti-histamine action and set up the dosing duration between 15 and 120 minutes in order to investigate the time-change. With regard to allergic rhinitis and immediate asthma reactions models, preliminary studies using a response curved surface model with parameters of the dosed amounts, dosing duration and efficacy were implemented. In these studies, allergic rhinitis showed a saddleback shaped curve. Therefore, the studies were carried out using the acute asthma model. The Evaluation Centre accepted the response.

As examples of pharmacological actions of fexofenadine, the selective antagonism of H_1 receptors, chemical mediator release suppression, inflammatory cytokine suppression, and eosinophil migration suppression were listed. The Evaluation Centre requested a discussion on the effects seen at the clinical dose, considering the potency observed in the efficacy pharmacological studies and the plasma free concentration achieved at the clinical dose.

The main action of the fexofenadine was histamine H_1 receptor antagonism because; the suppression of LT levels in BALF was observed at the higher oral dose (8.2mg/kg) than the suppression of histaminic wheals; the clinical dose suppressed approximately 25% of histamine release from human basophile, although IC_{50} for histamine release from human basophile and Cmax of oral dose in guinea-pigs were higher than the clinical plasma concentration (approximately two-hold concentration (1μM) of Cmax of the clinical dose (0.5μM) showed a significant inhibition); some tissues showed a higher intracellular concentration than the plasma concentration. However, the applicant declared that suppression of release of chemical mediators might be involved as a part of the clinical effect. The Evaluation Centre instructed that this should be reflected in the prescribing information appropriately.

F. Data on Absorption, Distribution, Metabolism and Excretion

For investigation of pharmacokinetics, un-labelled fexofenadine and ^{14}C-fexofenadine were used. Radiochemical purity of the ^{14}C-fexofenadine was 98.5%. The dosed amounts were expressed as free base.

(1) Results in animals

When rats were administered with the ^{14}C-fexofenadine intravenously (1mg/kg) or orally (2.5, 5.5, 10mg/kg), the plasma radioactivity concentration reached Cmax at 5 to 15 minutes after dosing, then showed the second peak at two hours after dosing, which suggested the presence of the enterohepatic circulation. The absorption rate of

fexofenadine was suggested to be approximately 30%, based on an amalgamated radioactivity excretion rate to the bile and urine of the rats. The ratio of AUC of radioactivity after oral and intravenous administration was between 3.5 and 3.8%. Neither food effects nor sex differences in plasma radioactivity concentrations in rats were suggested. In the absorption site study with rat gastrointestinal loop, fexofenadine showed the highest rate of absorption at the duodenum, then the absorption rate decreased in the following order of the jejunum and the ileum, the stomach and the colon. When a single dose of the un-labelled fexofenadine was orally administered, the plasma half-life was 2.9 to 5.0 hours for rats, 1.0 to 2.6 hours for guinea-pigs and 1.5 to 2.0 hours for dogs. When mice (30mg/kg), guinea-pigs (10mg/kg) and dogs (8.7, 27mg/kg) received a single oral dose, the bioavailability was 19, 19 and 44 to 57%, respectively.

When dogs were received oral repeated dose of 50 mg/kg of fexofenadine twice daily for 183 days, there was no difference in pharmacokinetic parameters at the initial administration or during repeated dose. It was concluded that the repeat dose did not affect pharmacokinetics. When rats received intravenous administration of the ^{14}C-fexofenadine (1mg/kg), the kidney and the liver showed the highest radioactivity at 15 minutes after dosing (36 to 43 times of plasma concentration). At 72 hours after dosing, radioactivity was detected only in the lung, the spleen, the testis, the kidney and the liver (less than 9ng eq./g). When rats received a single oral dose of the ^{14}C-fexofenadine at 5.5mg/kg, the majority of tissues showed the maximum concentration at one hour after dosing. In addition to the gastrointestinal tract, the concentration was high in the liver and the kidney, similar to when rats received intravenous dose. At 72 hours after administration, trace radioactivity was present in the lung, the testis, the kidney and the liver. Radioactivity was not detected in any other tissues. When pregnant rats were orally given the ^{14}C-fexofenadine (6mg/kg), transfer of radioactivity to the foetus was observed. The maximum concentration was about one sixth of the plasma radioactivity concentration of the dam.

The ratio of *in vivo* protein binding (20 to 5000mg/mL) in rats and dogs were 83 to 86 and 89 to 90%, respectively.

In rats, the majority of fexofenadine was present as the unchanged form in plasma, urine, bile and the tissues. The ketones, hydroxilated metabolites at the methyl bases, N-dealkylated metabolites, hydroxlated metabolite at the phenyl base and gluconate conjugate of hydroxylated metabolites at the phenyl bases were identified in plasma or urine. When 30μM of fexofenadine was incubated with rat liver microsome, the speed of metabolism of fexofenadine was very slow. When 30μM of fexofenadine was incubated with rat liver microsome, the speed of metabolism of fexofenadine was very slow. When rats received repeated oral dose of fexofenadine (30, 100, 300mg/kg) once daily for seven days, a slight reduction in O-deethlation of ethoxyresorufin was observed in the 100 and 300mg/kg groups compared with the control group. However, they recovered to the level in the control group after one-week washout. Few metabolites were present in dog plasma.

When rats received intravenous administration of the ^{14}C-fexofenadine (1mg/kg), 12.8% and 82.4% of the dosed radioactivity was excreted in the urine and faeces respectively, within 120 hours from dosing. When rats received oral dose (5.5mg/kg), 1.4% and 97.4% of the radioactivity was excreted in urine and faeces, respectively. When dogs received intravenous administration (1mg/kg), 17.6% and 78.1% of the administered radioactivity was excreted in urine and faeces, respectively. When 5.1mg/kg was orally administered to rats with bile duct cannulation, 27.5% of the radioactivity was excreted in bile, 2.5% in urine and 69.1% in faeces within 48 hours of administration. It was administered to the duodenum of different rats and the excretion rate to bile and urine were obtained. The result showed that at least 13% of the radioactivity administered was reabsorbed.

It was reported that radioactivity in milk reached the peak at four hours after administration when lactating rats received oral dose (6mg/kg). The concentration in milk was similar to the plasma concentration. An *in vitro* study with a section of the digestive tract of a rat suggested that fexofenadine was excreted from the digestive tract via the active transport system of p-glycoprotein. In an *in vivo* study in dogs, AUC of

fexofenadine was increased by erythromycin or ketoconazole. When the racemate and the optic isomers were orally given to guinea-pigs, xxxxx not xxxxx.

(2) Results in human

Pharmacokinetics of fexofenadine in healthy adult volunteers was investigated in Japan. Pharmacokinetics in healthy adults, elderly, rhinitis patients, urticaria patients, hepatically and renally impaired patients was investigated abroad.

When fasting healthy adult male volunteers received a single oral dose of 20, 60, 120 and 240 mg capsule of fexofenadine, Cmax was achieved at 1.9 to 2.2 hours after dosing and elimination half-life was 7.7 to 13.8 hours. The renal clearance was 2.99 to 4.43L/h. The unchanged form recovery rate from urine within 48 hours after a single oral dose at 120mg was 12.4%. From urine, 0.71% of a metabolite, xx M5 xx was recovered. When fasting healthy adult male volunteers received a single oral dose of a 20, 60, 120 and 180 mg fexofenadine capsule under the crossover method, Cmax and AUC were proportional to the dosed amount. When repeated administration of a 60 mg and 120mg fexofenadine capsule was given orally twice daily for seven days, plasma concentration reached the steady-state on two days after the start of dosing. It was concluded that the repeated dose did not affect the pharmacokinetics. Compared with terfenadine, AUC and Cmax of a dose of a 60mg fexofenadine round tablet after a meal were about a half of those of a dose of 60mg terfenadine and their renal clearance was similar.

When healthy adult male volunteers (overseas) received a single oral dose of the ^{14}C-fexofenadine solution at a dose level of 60mg, about 80% of radioactivity was excreted in faeces and about 11.5% in urine within 11 days of the dosing. The majority of recovered radioactivity was the unchanged form. When oral dose of 180mg racemate solution was repeatedly administered twice a day, the ratio of optic isomers in plasma was around 63:35 (+:–) and the ratio was almost unchanged regardless to time after administration. When a single dose of the ^{14}C-fexofenadine solution at a dose level of 60mg was orally administered, the ratios of optic isomers recovered from urine and faeces were almost the same.

The effect of food was investigated abroad. When healthy adult male volunteers received a single dose of 120mg tablets under fasting conditions or after a high fat meal using the crossover method, AUC and Cmax with meal were reduced by 15% and 14%, respectively. Healthy adult male and female volunteers (overseas) received repeated oral dose of fexofenadine solutions at dose levels of 40, 200 and 400mg twice daily for seven days. The Cmax and ACU were higher in female than in male but a difference in the renal clearance was not observed. When elderly males and females of 65 years old or above, renally impaired patients and hepatically impaired patients received a single oral dose of 80mg fexofenadine capsules, plasma concentrations of elderly subjects and renally impaired patients increased compared with healthy adult subjects. It was reported that no clear difference was seen from the severity (Child-Pugh classification) among hepatically impaired patients. Population pharmacokinetics (population PK) of rhinitis patients who received repeated dose of 40 to 240 mg capsules twice daily and urticaria patients who received repeated dose of 20mg to 200mg oblong shaped tablets twice daily were investigated. It was concluded that there was no large difference in their PK from the PK of healthy adults. In an investigation of PK from single dose studies of fexofenadine 20 to 240mg capsules in Japan and abroad, about 20 to 35% differences were seen in PK parameters. The applicant concluded that the difference in plasma concentration by sex and race was due to the differences in the body-build, such as bodyweight.

When 40, 200 and 400mg of fexofenadine was orally administered to healthy adults, the plasma protein-binding rate of fexofenadine at one hour and 12 hours after dosing was between 60 and 82%. The metabolising speed of fexofenadine by human liver microsome was considered to be very slow.

Drug interactions were investigated in Japanese healthy male volunteers using the crossover method, and the subject received fexofenadine alone (repeated oral dose of 120mg round tablets twice daily for seven days), erythromycin alone (repeated oral dose of 300mg four times daily for seven day) and a combination of the two agents. When erythromycin was used in combination, fexofenadine Cmax and AUC increased by

twofold compared with fexofenadine alone. The amount excreted in urine at 12 hours from the final dose also increased by 2.3 times. In contrast, there was no effect of fexofenadine in a plasma concentration of erythromycin. Similarly, in the overseas combination studies with erythromycin or ketoconazole, a similar degree of increases in fexofenadine plasma concentration and a similar level of excretion in urine were observed. Comparison of PK after administration of fexofenadine 120mg capsules as a monotherapy and as a combination therapy with an aluminium hydroxide gel/magnesium hydrate preparation (20mL, 15 minutes before administration of fexofenadine) or omeprazol (20 and 40mg, 11 hours and one hour before administration of fexofenadine) showed reductions in plasma fexofenadine concentrations when an aluminium hydroxide gel/magnesium hydrate preparation was administered concomitantly. However, it reported that there was no effect on PK of fexofenadine when omeprazol was administered concomitantly.

Bioequivalence studies were carried out abroad using 60mg capsules (the identical formulation to the capsules used in Japanese phase I studies), 60mg round tablets (the identical to the tablets used in Japanese phase II studies) and 60 mg oblong tablets (the tablets to be marketed). All the capsules and the oblong tablets, the round tablets and the oblong tablets were considered to be bioequivalent.

The Evaluation Centre mainly reviewed the following points.

The applicant positioned the PK studies and drug interaction studies in the healthy adult volunteers as a component of the Complete Clinical Data Package and presented the results obtained from overseas studies as data on effect of food on PK and bioequivalance data in men, therefore, the Evaluation Centre asked for an explanation of effects of the ethnic factors on PK including description of analysis methods used in comparison. The applicant explained the study methods used for comparison, background factors of subjects and the detailed process of structuring the architecture of the population PK model in relation to comparison of PK study results in healthy adults. They also presented results of an investigation of PK parameters without using the model. They concluded that results from both analysis were the same. In response to

instruction on background factors in PK parameters, they replied that mixed effect nonlinear regression analyses was carried out for each patient's PK parameters using a method independent of the model in order to review the background factors. The Evaluation Centre requested a rationale for deciding that they can make a pharmacokinetic estimation only from the investigated variables (age, bodyweight, race and dose). They responded that they chose studies that used capsules and administration under fasting conditions, and smoking, consumption of alcohol, concomitant use of other drugs were prohibited during the trial period, and the body build can be discussed in context of body weight as the definition of obesity was provided. The Evaluation Centre pointed out that a crossover study in Japanese volunteers was not implemented and a comparison of effects of food on PK in different subjects showed larger effects than the effects seen in the food effect studies carried out abroad. The applicant presented all crossover study results (four studies) that were investigated the food effect with various formulations and results of similar comparisons in different subjects. They explained, in the crossover studies, the food effect on AUC was relatively constant 17 to 24%, and inter-subject and inter-study comparisons showed 31 to 47% reductions, which were similar to results in Japanese (42% reduction). They also presented a response that types of food would not have a large effect considering physiochemical characteristics of fexofenadine and the effect of food on PK in Japanese was considered the same as that in the overseas population. Considering the above review result, statements on the food effect studies implemented abroad and the results of the review in Japanese were added to the prescribing information. Furthermore, the various dosage forms used in PK investigations were clarified in the Gaiyo and an explanation on bioequivalence of the various formulations (dissolution studies, human studies) was added.

With regard to absorption of fexofenadine, the Evaluation Centre asked for an explanation of the involvement of p-glycoprotein in the absorption process. The applicant's response was that fexofenadine was excreted to the cavity of the digestive tract by active transport of p-protein and they believed the mechanism of drug interactions with concomitant use of erythromycin etc., was caused by an inhibition of p-glycoprotein leading to an increase in the transportation to the blood and an increase in the plasma fexofenadine concentration. This was supported by results from p-

glycoprotein investigation with fexofenadine and a literature search, which suggested the presence of the active transport system because the permeability from the blood vessel into the cavity was high in the digestive tract segment *in vitro* study system in rats; the active transport disappeared in the presence of verapamil; the fexofenadine plasma concentration was increased when erythromycin or ketoconazol was administered concomitantly in the dogs and human *in vivo* studies. The Evaluation Centre also requested discussion on differences in bioavailability by species. They replied that the studies on excretion to the urine and faeces in dogs and rats and the study on excretion to the bile in rats suggested that the most of fexofenadine was excreted to the faeces via the liver without being metabolised, and bioavailability in rats, guinea-pigs and dogs was 3.5 to 3.8%, 19% and 44 to 57% respectively, and the bioavailability in human was estimated at 33% from the radio-labelled terfenadine study and a comparison of AUC of oral terfenadine and fexofenadine. The absorption rate in rats was about 30%, and a comparison with the bioavalability suggested the presence of a very strong first pass effect. In other species, direct investigations into the absorption rate and the first pass effect were not carried out. They explained, however, as fexofenadine was excreted to the faeces via the liver and the absorption rates in other species were estimated at 30 to 50% based on their clearance and hepatic blood flow, the differences in bioavailability may be due to the differences in the first pass effects.

The Evaluation Centre also instructed the applicant to reflect PK study results to the prescribing information. In a section under Pharmacokinetics, the results of the PK studies in elderly carried out abroad had been described in the PI. The applicant added a description on the degree of changes in the PK parameters compared with the younger generation. Also, a section of "Elderly Patients" were added under Precautions for Use. Regarding patients with hepatic and renal impairment, the applicant reviewed the PK parameters and lab test values. In their response they stated that there was no particular safety issues in subjects with high Cmax and AUC. The description on PK of patients with renal impairment was amended to clarify a relationship of PK and creatinine clearance. Regarding drug interactions, the Evaluation Centre instructed the applicant to describe the suspected mechanism and the effects on the PK parameters, etc., in Precaution for Use. They replied that they will not set up a section for interaction in

Precaution for Use but they will put that in Other Precautions, because there was no significant finding from the interaction studies with erythromycin, etc., other than an increase in the fexofenadine blood concentrations; adverse drug reactions, lab test abnormalities and ECG were not affected; no clinical data or post marketing adverse drug reaction reports can clearly demonstrate the interactions; the results from concomitant use with the aluminium hydrate/magnesium hydrate preparation were expected from the physiological characteristics.

Regarding the provision of information on drug interactions in the PI and drug interactions involving p-glycoprotein, the applicant stated that no safety issues were highlighted in the interaction studies in healthy adult. However, the plasma concentration of fexofenadine showed a significant increase. Therefore, the Evaluation Centre believed that these points should be reviewed in post marketing surveillance, but these required a discussion by the expert committee.

G. Data on Results of Clinical Trials

Overview of Submitted Data

Clinical study results submitted were compiled to show the results of overseas studies were extrapolatable to Japanese patients. In Japan, pharmacokinetic data was gathered in phase I studies, etc., and study data showing dose responses in chronic urticaria and allergic rhinitis was gathered in phase II studies.

1. Phase I studies

Placebo controlled single dose (20, 60, 120, 240mg) and repeated dose (60, 120mg twice daily for seven days) studies were implemented in healthy adult male volunteers. One subject who received a single dose of 240mg showed transient increases in GOT, GPT and LAP. One subject who received repeated dose showed adverse events such as

headache and sleepiness and elevated GOT and GPT, which were mild and transient. The tolerability was considered to be good.

Results on pharmacokinetics of fexofenadine were also collected. They were used as comparative investigation data with PK of the overseas population (see section F).

2. Clinical pharmacological studies, etc.

a. Intradermal histamine test

An intradermal histamine test, which has been used for investigation of effects and duration of the effects of histamine H_2 receptor agonists, was carried out in order to investigate the inhibitory action on skin wheal and erythema after histamine injection xxx. When a single dose (20, 60, 120, 180mg and placebo) was administered under fasting conditions using the cross over method, dose dependency in the wheal/erythema inhibitory action was observed. However there was not a big difference above 60 mg. When a single dose of fexofenadine (60 and 120mg) and 60mg terfenadine were administered after a meal using the cross over method, AUC of 60 mg fexofenadine was about a half of 60mg terfenadine and the wheal/erythema inhibitory action of 60mg fexofenadine was 0.7 to 0.8 times of 60mg terfenadine.

The wheal/erythema inhibitory action was investigated abroad in a single dose study (xxx 10 to 800mg), a repeated dose study (xxx 20 to 690mg twice daily for 29 days) and a comparative study with ferfenadine (xxx 60 and 180mg). When Japanese and overseas results were compared, inter-subject variations were considered to be large in the both populations, racial differences were relatively small and response, etc., were similar.

b. Pollen exposure test

Allergic rhinitis patients in a room sprayed with ragweed pollen received a single dose of 60mg and 120mg of fexofenadine. Compared with placebo, fexofenadine showed a

significant suppression of the symptoms. Time to reaction at a dose level of 60mg was less than 60 minutes and the effect was still maintained after 300 minutes.

c. Effect on the central nervous system

In patients with ragweed allergy, an effect of a fexofenadine 60mg single dose on the central nervous system was investigated using automobile simulation xxx. The effect of fexofenadine was significantly smaller compared with 50mg of diphenhydramine and had no difference with placebo.

A word processor imputing study in healthy adult volunteers investigated the effect of 120 fexofenadine in Japanese xxx. The effect of fexofenadine on psychomotor ability was similar to placebo and significantly weaker than 6mg d-chlorpheniramine maleate.

d. Effect on ECG

In Japan, effects of drug interactions of fexofenadine and erythromycin on ECG were investigated xxx. With repeated doses of concomitant fexofenadine (120mg, twice daily for seven days) and erythromycin (300mg, four times daily for seven days), the plasma concentration of fexofenadine showed an approximately twofold increase in AUC and Cmax, compared with when fexofenadine was administered alone. However, 12 lead electrocardiographs did not show effects from the concomitant use and tolerability of the concomitant use was good.

An erythromycin/ketoconazol drug interaction study xxx, a repeated dose study with 400mg fexofenadine twice daily xxx and a comparison study with terfenadine were implemented abroad to investigate the effect on pharmacokinetics and ECG. In these studies, an effect of fexofenadine on ECG was not observed.

e. Elderly, renally /hepatically impaired patients

When elderly people who were over 65 years old, renally impaired and hepaticaly impaired patients received a single dose of 80mg fexofenadine in oversas studies, no adverse drug reactions concerns were observed (see section F for PK).

3. Phase II studies in Japan

a. Dose selection studies in chronic urticaria

Targeting 266 patients with chronic urticaria, a double blind dose selection study with fexofenadine 10, 60 and 120mg twice daily for one week was implemented. The primary endpoint was the amount of changes in total symptom scores (itching and rash) of patient's diary before and after dosing. Due to protocol violations, etc., 12 subjects were excluded from the analysis.

The results showed a significant decrease in symptom scores at the dose levels of 60mg and 120mg compared with 10mg. There was no big difference between 60mg and 120mg. The most common adverse drug reactions were sleepiness and malaise at any dose levels, but no dose dependency in occurrence of adverse events was observed. Therefore, recommended dose was considered to be 60mg twice daily.

Results from dose comparison studies in chronic urticaria in Japan and abroad were compared. There was no interaction in the quantities of changes in symptom scores between studies and there was no difference in detail of adverse events and adverse drug reactions. It was concluded that there was no difference in dose responses of the Americans and Japanese.

b. Dose selection studies in allergic rhinitis

Two dose selection studies in allergic rhinitis were implemented in Japan.

A phase II double-blind dose selection study with fexofenadine 10, 60 and 120mg, twice daily for two weeks was implemented targeting 305 patients with perennial allergic

rhinitis (of those, 252 cases were included in the primary analysis) xxx. The primary endpoint was the amount of changes in the total symptom scores (sneezing, nasal discharge, nasal congestion) in the patient's diary before and after dosing. Results showed an improvement of symptom scores in all dosed groups, but a dose response was not observed.

Among the background factors, there was a bias in the severity. Moderate cases were the most common in the 10 mg group. Stratified analysis by severity showed a dose response in severe cases, suggesting the recommended dose to be 60 mg. However, in moderate cases, the 10mg group showed the biggest score reduction and a dose response was not observed. There was no difference in the occurrance of adverse events among doses. Also, symptoms that cause concerns were not observed. The common adverse drug reactions were sleepiness, dry month and headache.

In this study, the results did not show a clear dose response. Therefore, an additional study in patients with seasonal allergic rhinitis (cedar pollen allergy) was implemented referring to an overseas study protocol.

A phase III double blind dose comparison study in 310 seasonal allergic rhinitis patients (cedar pollen allergy) who received 60, 120mg fexofenadine and placebo, twice daily for two weeks was implemented xxx . The primary endpoint was the amount of changes in total symptom scores (sneezing, nasal discharge, nasal congestion) in the patient's diary before and after dosing. Results showed a dose response. Placebo did not show any reduction in scores, whereas the 60mg group and the 120mg group showed a similar degree of score reductions. The 60mg group showed a significant reduction in scores compared with the placebo group ($p=0.0244$), however, the amount of changes in the 120mg group was not significant ($p=0.0561$). There was no difference in the occurrance of adverse drug reactions between the placebo group and active drug groups. Symptoms that cause concerns were not observed. Therefore, a 60mg twice daily was considered to be the recommended dose.

The results from the dose comparison studies in seasonal allergic rhinitis in Japan and abroad were compared. No interaction between the amounts of changes in symptom scores of the studies was observed. There was no difference in detail of adverse events and adverse drug reactions. It was believed that there was no difference in the dose responses in Americans and Japanese.

4. Overseas phase II/IV studies

a. Chronic urticaria

In the USA and Canada, two double blind dose comparative studies with fexofenadine 20, 60, 120, 240mg and placebo twice daily for four weeks were implemented to investigate the recommended dose for chronic urticaria (xxx 892 cases in total). The efficacy endpoint was the amount of changes in symptom scores (itching and wheal) before and after dosing in the patient's diary. Compared with placebo, fexofenadine at all dose levels showed significant reductions in the itchiness score, which was the primary endpoint. The reductions seen in three doses above 60mg were significantly bigger than 20mg and there were no differences among those three doses. No dose dependency in the occurrence of adverse drug reactions (adverse events with relevancy to a trial drug that can not be ruled out) was seen. The incidence of adverse drug reactions was 24.4% in total in the fexofenadine groups and 25.3% in the placebo group. There was no difference between fexofenadine and placebo. The most common adverse drug reaction of fexofenadine and placebo was headache. Adverse drug reactions that were more common in fexofenadine groups compared with placebo were insomnia and somnolence. Results from the study did not show differences in efficacy and safety in doses above 60mg. Therefore, the recommended dose was considered to be 60mg, twice daily.

b. Allergic rhinitis

To investigate the recommended dose for seasonal allergic rhinitis, two placebo controlled double blind dose comparison studies were implemented in autumn (main

antigen: ragweed) in the USA (xxx, 1,160 cases in total). The patients received 40, 60, 120 and 240mg of fexofenadine or placebo twice daily for two weeks. The efficacy primary endpoint was the amount of changes in the total symptom scores (sneeze, nasal discharge, itchy nose/palate/throat, itchy/watery/bloodshot eye) in the patient's diary before and after administration. Fexofenadine at any dose levels showed significant reductions in the symptom scores compared with placebo. Doses above 60mg showed significant reductions in the symptom scores from the initial administration but manifestation of the effect at 40mg was slow. The amount of changes in the symptom scores at 60mg was not different from 120mg and 240mg. No dose dependency was observed in the occurrence of adverse events/adverse drug reactions. The incidence of adverse drug reactions was 12.3% in the fexofenadine groups in total and 11.4% in the placebo group, showing no difference between fexofenadine and placebo. The most common adverse drug reaction of fexofenadine and placebo was headache. It was concluded that 60mg twice daily should be the recommended dose.

In spring seasonal allergic rhinitis (main antigen: grass and tree pollen) patients in the USA and Canada, two double blinded comparative studies with fexofenadine (60mg, twice daily) and loratadine (10mg, once daily, not approved in Japan) for two weeks were implemented (xxx 901 cases in total). There was no difference in reductions in the total symptom scores of both groups and the amount of changes was similar to the above-mentioned study. The incidences of adverse drug reactions were similar, 9.8% with fexofenadine and 11.1% with loratadine. The most common adverse drug reaction of fexofenadine was headache and that of loratadine was somnolence and headache.

In Canada, fexofenadine 60mg twice daily and 120mg once daily for four weeks were compared with placebo in 673 patients with perennial allergic rhinitis (main antigen: house dust mite, fungus, etc.) in a double blind fashion xxx. Compared with placebo, the symptom scores were significantly decreased with twice daily administration of 60mg. However, 120mg once daily administration did not show a significant difference. The most common adverse drug reaction was headache in all dosed groups and there was no difference in the incidences of advises drug reactions among these three groups.

It was concluded from those results that twice daily administration of 60mg of fexofenadine was useful against allergic rhinitis from various antigens.

5. Long term studies

In the USA, placebo controlled double blind comparative studies in healthy adult male and female volunteers who received 60 mg fexofenadine twice daily for six month (xxx) and 240mg once daily for 12 month (xxx) were carried out to investigate safety. In those studies, fexofenadine and placebo showed no differences in adverse events, lab test results and the occurrence of ECG abnormalities, demonstrating long-term safety.

6. Investigation of extrapolatability of overseas clinical data

Use of terfenadine and other similar drugs in Japan and overseas countries, their pharmacokinetics and pharmacodynamics of fexofenadine were compared. The effects of ethnic factors on fexofenadine were considered to be small. The efficacy results from the Japanese dose selection study and the overseas dose comparison studies in chronic urticaria showed a similar dose response of fexofenadine. The results from the Japanese dose comparison study and the overseas dose comparison studies in seasonal allergic rhinitis also showed a similar dose response. No large differences in safety in both diseases were seen between the Japanese studies and the overseas studies. Based on these similarities, extrapolation of the overseas data to the investigation of efficacy and safety in allergic rhinitis and urticaria in Japan was considered possible.

7. Adverse drug reactions and abnormal lab test values

Pooled analysis of the nine overseas double blind studies with twice-daily administration (20 to 240mg/dose) showed no difference in the incidence of adverse drug reactions between fexofenadine and placebo: 14.6%(563/3,845) for fexofenadine and 15.2% (164/1,078) for placebo. Dose dependency was not observed. In pooled analysis of 13 studies including overseas once daily administration double blind studies (60 to 240mg, once daily), the incidence of adverse drug reactions was 14.5% (899/6,152). In the

Japanese double blind studies, the incidence of adverse drug reactions with fexofenadine was 22.3% (164/734). There was no difference from the incidence of adverse drug reactions in the Japanese placebo controlled double blind study: 10.3% (21/203) for fexofenadine and 7.5% (8/107) for placebo. The most common adverse drug reactions seen abroad were headache, nausea and sleepiness and their incidences were not different from placebo. The most common adverse drug reactions in Japanese subjects were sleepiness, headache, dry mouth and malaise. The symptoms observed were not different from symptoms seen abroad.

The incidence of changes in the lab test values and the outliers seen in the overseas clinical studies were not different from the placebo. Also in the Japanese clinical studies, abnormal findings in the lab test values that cause concerns were not observed.

Summary of evaluation by the Evaluation Centre

(1) Assessment of efficacy (mainly regarding the acceptability of bridging)

With regard to the efficacy of fexofenadine in the filed indications, the applicant claimed that clinical trial results which were the approval base in several overseas countries (see "overview of submitted data") could be used for the efficacy (and safety) evaluation in Japan if a concept of creating a bridge using the Japanese dose selection studies was applied.

The Evaluation Centre believed that they could accept overseas efficacy/safety data as a part of the Japanese submission, providing overseas clinical study results were the approval base of efficacy and safety in the respective countries (region), they were treated as approval application data in each country (region) and the concept of bridging was successfully applied. Therefore, when the Evaluation Centre was evaluating the efficacy of fexofenadine, the main discussion was focused on whether bridging was acceptable.

Figure. Complete Clinical Data Package of Fexofenadine

1) Appropriateness of the bridging study in allergic rhinitis (assessment of the new study in allergic rhinitis)

In the original application, the applicant claimed the Japanese data and the overseas data can be bridged using the results of those studies and the overseas study results in chronic urticaria and seasonal allergic rhinitis, based on the phase II dose selection study in chronic urticaria (J201; xxx) and the phase II dose selection study in perennial allergic rhinitis (J202; xxx).

However, the Evaluation Centre judged it was impossible to evaluate use of fexofenadine in allergic rhinitis from the submitted data alone, because data from studies were insufficient. The examples were; the 10mg group (20mg/day), the 60mg group (120mg/day) and the 120mg group (240mg/day) of the study J202 did not demonstrate dose relationships in the improvement in the nasal symptom scores, which was the primary endpoints of the study, as well as in the improvements of the various symptoms scores and the daily life disruption scores, the overall improvement rate and patients impressions, which were the secondary endpoints.

The Evaluation Centre decided not to review the bridging because; i) the study J202 investigated three doses of 10, 60 and 120mg, but it did not show differences in the treatment effect between groups and it was unable to support the selected clinical recommended dose and ii) it was impossible to compare the overseas and Japanese studies because of the difference in the definition of the assessment variables and the selection criteria of the overseas and Japanese studies. Especially, for the former, there were interactions between severity at the start of the treatment and the effect of the treatment in the overseas studies. Therefore, the Evaluation Centre believed the bias in the severity at the start of the treatment among the groups had a large effect on the results of the study J202 and made assessment/interpretation of the study results ambiguous.

The applicant concluded that they could not support the recommended dose for allergic rhinitis only from the Japanese J202 study and were unable to bridge overseas data. They implemented a new additional study (phase III placebo controlled double-blind dose comparison study in seasonal allergic rhinitis patients: J3106 xxx). This study targeted patients with seasonal allergic rhinitis, as with the studies carried out abroad. They set the definition of the assessment variables as close as possible to the definition used in the overseas studies and implemented the study in eight centres. It compared three groups receiving placebo, 60mg and 120mg and used a study design with stratified allocation based on severity before treatment. The result showed clear differences in the treatment effects between the placebo group and the 60mg group and demonstrated a similar dose-response relationship to that seen in the overseas studies. The Evaluation Centre concluded that it was possible to bridge the allergic rhinitis data with the overseas data, as with the urticaria data, and it was appropriate to choose 60 mg as the recommended dose.

When designing the additional study, stratified allocation was put into place because the severity at the start of the treatment largely influenced the treatment effect. As a result, the study showed the same trend as the trend seen in the overseas studies. However, currently, it is not possible to find out a detailed cause of the relationship between the severity and the treatment effects, which has been observed in several studies, and give a scientific explanation. The Evaluation Centre believes investigations into this issue should be continued in future.

2) Appropriateness of the bridging study for chronic urticaria

a) Appropriateness of steps taken for review of bridging

The Evaluation Centre asked whether the phase II dose selection study (J201;xxx) in chronic urticaria was designed with bridging in mind. They also asked for the applicant's understanding of criteria that would support a claim of similarity between the western population (the studies implemented in the US and Canada were included in "Complete

Clinical Data Package") and the Japanese population when planning the study, if the applicant was thinking about bridging beforehand.

The applicant replied that they were not intending to position the study J201 as a bridging study when they were planning the study (year xxxx). However, based on consultations with the Organization for Pharmaceutical Safety and Research (hereinafter referred as "Kiko") on dd, mm, yy, they decided to position this study as a bridging study and produced an additional statistical analysis plan on dd, mm, yy, that was before the key break on dd, mm, yy. Furthermore, they replied that when reviewing a similarity, the following the stapes were discussed during production of the statistical analysis plan. However, xxx
xx for efficacy bridging, xxx
xxxxx for safety bridging and a comprehensive clinical interpretation was mainly used for an assessment of the overall bridging. The Evaluation Centre accepted the response.

(Bridging procedures and decision making criteria used by the applicant)

xxxxxxxx

c. Comparability of duration of the treatment and selection criteria (especially assessment criteria of wheal)

The applicant was asked to provide an explanation on suitability of the study J201 as a bridging study from the following points. In the discussion of extrapolation of the overseas clinical studies, the applicant was asked to clarify comparability of the overseas studies and the Japanese study by confirming the similarity of (1) the inclusion/exclusion criteria, (2) the trial environments such as concomitant medications, (3) the assessment scales and the assessment (analysis) methods of the primary endpoints, (4) the sizes of the inter-patient variations (5) the duration of fexofenadine treatment.

To this instruction from the Evaluation Centre, the applicant gave the following explanations.

(1) Inclusion criteria: In a rigorous comparison, differences in the age range and the degrees of urticaria symptoms were found. Even though there was a difference in the age range of inclusion criteria for the Japanese and overseas' studies, the proportion of recruited patients who were outside of either one of the age ranges was small. The applicant's opinion was that there was no problem in comparing the studies. The Evaluation Centre accepted the opinion.
With regard to the degree of symptoms, in the overseas studies, patients with TSS (Total Symptom Score: a total of scores for a degree of itching in a 12-hour period prior to the observation and a number of wheal (urticaria) in the same period, which were determined separately) three or over were included. In the Japanese study, patients with "symptoms that were severe enough for evaluation of the trial drug (excluding minimum pruritus or eruption)" according to the investigator's diagnosis were recruited. TSS 3 or over meant that the itchiness score was 2 (irritating, some interference with everyday activities or sleep) or over (score 1 is mild itching, hardly noticeable, not irritating) and the wheal score was 1 (wheal in one to five places) or over (score 0 is wheal absent). Japanese inclusion criterion, "excluding minimum" was almost the same as TSS 3 or over in the overseas studies, because those patients had a symptom severe enough to evaluate efficacy. The applicant concluded, therefore, that those differences in the selection criteria would not affect the efficacy assessment and the Evaluation Centre accepted the response.

(2) Prohibited concomitant medications: The applicant responded, in the Japanese study, that prohibited concomitant medications were defined according to the rules used in the overseas' studies and patients who used drugs that may affect efficacy evaluation were excluded. They believed that the effect from the use of prohibited concomitant medications was removed from all studies equally. The use of prohibited concomitant medications was largely different, 22 patients (10.3%) used a prohibited concomitant medication in the Japanese study, whereas overseas 318 patients (76.1%) in the study PJPR0039 and 340 patients

(77.5%) in the study PJPR0067 used such a medication. However, most of concomitant medications taken in the overseas studies were vitamin preparations. They argued these drugs do not have effect that influence the efficacy assessment of fexofenadine in chronic urticaria and, for investigating the effect on chronic urticaria, treatment environments of concomitant medications were comparable in the Japanese and overseas' studies. The Evaluation Centre accepted these responses.

(3) Assessment criteria of the symptom scores: In Japan, patients assessed itchiness during day from how itchy they felt and how they scratched, and itchiness during night from the degree of itchiness during night and the effect on night-time sleep. In the overseas studies, patients made an overall severity assessment based on interruption of everyday life and sleep. The applicant argued that even though these standards had slight differences, they were qualitatively similar and, therefore, no large differences in the substance of the assessments would be caused. Also there was a difference in the assessment of rashes. In the Japanese study, patients observed redness and swelling and they made an overall assessment. In the overseas' studies, it was assessed by the number of rashes/wheals (a rash was not included in the primary endpoints in the overseas' studies, therefore, not used in bridging). The applicant argued, even though there was a difference, it was possible to compare improvement effects at each dose, because both the Japanese and overseas' studies assessed changes in the itchiness scores. Those replies were accepted by the Evaluation Centre. The assessment (analysis) methods of the primary endpoints were considered almost identical as the amount of changes in the scores was used in all studies. However, the way the data was handled in calculating the amount of changes in the itchiness scores differed in the Japanese and overseas studies. When reviewing the bridging, the applicant handled data of the primary endpoint in the same way for all studies, so that the changed amounts in the itchiness scores can be compared using the values at the same time point and calculated in the same way (mean itchiness scores at week 1 of the administration were analysed by FAS). The Evaluation Centre accepted the response.

(4) The range of itching and rash scores before treatment: The range of the scores prior to the treatment was roughly the same in all three studies. The range of the changes from pre-treatment values to post-treatment values ws also similar. The Evaluation Centre accepted the response of the applicant's conclusion that inter-patient variation in all studies was roughly the same.

(5) Duration of the treatment in the Japanese study: The applicant's responses were as follows. One-week was chosen for the treatment period in the Japanese study, considering the clinical experience of fexofenadine and similar drugs in Japan and overseas countries, and the treatment period when terfenadine was developed, and to set-up a duration in which effects of drugs can be observed. The duration of treatment in the overseas studies was set at four weeks because of the result of a negotiation with the FDA. In the overseas studies, week by week analysis showed a significant effect of fexofenadine compared with placebo at Week 1 and the significant effect was maintained from Week 2 to Week 4. However, the scores in the placebo group also decreased gradually by time. Therefore, the applicant believed that the efficacy of fexofenadine should be assessed on the first week of the treatment, when assessment was not affected by a factor such as spontaneous remission. Regarding efficacy, the applicant responded that a comparison of the Japanese and overseas studies was possible, because it was possible to use assessments made on the first week in all studies despite the difference in duration of the treatment in the Japanese and overseas studies. The Evaluation Centre accepted the response. Regarding safety, many of adverse events in the overseas studies appeared on the first week of the treatment, few adverse events appeared with a longer treatment and no particular adverse events had an increase in the incidence. Therefore, the applicant concluded that they can compare safety of the Japanese and overseas studies. The Evaluation Centre accepted the response.

3) Extrinsic factors

In the original approval application data xxx, the applicant only gave the following brief discussion on extrinsic factors in "review of effects from ethnic factors". For allergic rhinitis treatment, they stated, "For both perennial and seasonal rhinitis, nasal inhalation

preparation of steroid or disodium cromoglyate (DSCG) and oral anti-allergic agents with anti-histaminic actions have been used in Japan and overseas." For allergic skin diseases such as urticaria, they stated, " both in Japan and abroad, anti-histamine preparations are widely used and drug treatment in Japan has no fundamental difference from the West. Also we believe Japan and the West have no fundamental difference in diagnostics and test methods for the diseases." The Evaluation Centre asked the applicant to present on the fact that there was no difference in diagnosis/test methods, drug treatments and other treatments in Japan and abroad by showing Japanese and overseas' treatment guidelines, text books, summary of articles, etc. The Evaluation Centre also asked to indicate an absence of differences in clinical use of oral anti-allergy drugs in Japan and abroad.

The applicant presented various specialised books, summaries of articles from peer-review journals, data on use of various anti-allergic drugs in the major countries (the USA, the UK, France, Germany) and replied that there was no difference in Japanese and overseas diagnosis/test methods, drug treatments and other treatments.

Also regarding use of oral anti-allergy drugs; the second-generation anti-histamine agents were more widely used as treatments of allergic rhinitis and chronic urticaria in clinical practice than the first-generation (the drug classification in Japan classifies the second-generation anti-histamine as "449, other anti-allergy agents") both in Japan and overseas; other anti-allergy agents such as mediator release inhibitors (tranilast, pemirolast), a cytokine inhibitor (suplatast tosilate), a thromboxian A2 receptor inhibitor (seratrodast), a leukotrien receptor inhibitor (pranlukast hydrate), thromboxian A2 synthesis inhibitor (ozagrel hydrochloride) were not approved abroad and the amount used in Japan was still relatively small. The Evaluation Centre accepted the reply.

4) Appropriateness of positioning the interdermal histamine studies as bridging studies

The applicant discussed the relationship of plasma MDL16,455 concentrations and inhibition rates of areas of wheal or erythematic induced by administration of histamine

by analysing data from the interdermal histamine studies in healthy volunteers carried out in Japan and abroad (Japanese J003 xxx ; overseas PJPR0002 xxx) using the sigmoid Emax model. However, positioning of the interdermal histamine studies in bridging and the significance of the results were unclear, therefore, the Evaluation Centre asked the applicant to provide the details.

The applicant replied that pharmacodynamic comparison using the sigmoid Emax model in the reference data xxx was additional (post-hoc) analysis of the clinical efficacy only presented as an addition/reference. The conclusion obtained from this additional analysis was "compared with inter-subject varieties, racial differences were relatively small" because descriptive statistic values and graphs showed large variations amongst subjects and, compared to these variations, the average dose-response curves were near to each other. The Evaluation Centre accepted the response.

As stated by Monroe et al (J Allergy Clin Immunol 99:S798-806, 1997), an interdemal histamine study is only a provisional study of a dose-response relationship. The Evaluation Centre thinks this should not be used for estimating clinical efficacy of an anti-histamine drug in allergic rhinitis or chronic urticaria, and for comparing clinical efficacy of various anti-histamine drugs. The Evaluation Centre believes an interdermal histamine study on its own should not be used as a bridging study. In the expert discussion, appropriateness of such discussions and decisions needs to be reviewed.

(2) Assessment of safety

1) Long term safety

The Evaluation Centre questioned if Allegra tablets were used indefinitely after launch, will safety in long term administration be assured only with the overseas long term study in healthy adult male and female volunteers (PJPR0027 xxx, 12-month long term study: seven out of 240 volunteers who received fexofenadine and five out of 237 volunteers who were in the placebo group were Asians; implementation period mm, yy to mm, yy) and the 6-month long term study (PJPR0031 xxx; two out of 220 volunteers who

received fexofenadine and five out of 216 volunteers who were in the placebo group were Asians; implementation period mm, yy to mm, yy).

According to the data from the Japanese post marketing surveillance of terfenadine of 62,729 cases (included in efficacy evaluation: 21,619 cases of allergic rhinitis, 10,898 cases of urticaria, 27,233 cases of skin pruritus, etc., 2,979 cases of bronchial asthma), the percentage of patients who used terfenadine for six to 12 months was 1.2% in total (758/62,729); allergic rhinitis 0.6% and urticaria 1.1%. Patients who used terfenadine for more than 12 months were 0.3% in total (181/62,729), 0.1% for allergic rhinitis, 0.2% for urticaria. The also stated a Japanese clinical specialists' opinion that the most of allergic rhinitis and urticaria symptoms improves with less than one month of treatment, the treatment completes within two to three months at the longest, long-term treatment exceeding six months is rare and the dose is often reduced or intermitted once symptoms are improved. The applicant argued that because such a small number of patients received long-term treatment in clinical practice, implementing a long-term study in allergic rhinitis and recruiting the number of patients required by the guidelines was very difficult. They also responded that unnecessarily continuing treatment in patients whose symptoms were improved was not possible and even if a trial was carried out, they expected the majority of patients would withdraw/dropout within one to two months. The reason for using healthy volunteers in the long-term study in the USA was that they considered the study would be difficult considering compliance to the protocol and medical ethics. The Evaluation Centre accepted the reasons for not implementing a long-term study in Japanese patients. However, they asked with what data the applicant assured long-term safety of fexofenadine.

The applicant showed pooled analysis of incidences of adverse drug reactions by cumulative treatment duration of 65,903 patients of the terfenadine Japanese post-marketing surveillance. (The number of patients mentioned here was those included in safety assessment. Previously mentioned 63,729 cases were the number of patients included in efficacy evaluation.) Of 533 (0.8%, 533/65,903) patients who developed adverse drug reactions, 363 patients developed the first adverse drug reactions within seven days of cumulative use, 72 patients between one week to two weeks, 49 patients

between two to four weeks, showing about 91% (484/533) of patients with adverse drug reactions developed the reaction within one month of cumulative use. Newly observed adverse drug reactions after eight days were nausea in three patients, esdonophilia in two patient and finger tremor, numbness of finger/upper limbs, hypotension, breathlessness, difficulty of expectoration, period pain, hot feeling of chest, increased bodyweight, slight fever, swollen feeling, gastrointestinal disturbance and elevated GOT/GPT in one patient each. Considering 60mg terfenadine showed a similar blood MDL16,455 concentration to fexofenadine 120mg, those patients who received long-term treatment with terfenadine can be considered to have had as longer exposure than the exposure from long-term treatment with fexofenadine. Therefore, they concluded, no serious issues on safety of long-term fexofenadine treatment were expected from those safety data in long-term administration of terfenadine for allergic rhinitis, urticaria, etc.

Adverse drug reactions and abnormal lab test values from overseas clinical trials in the "Complete Clinical Package", namely, the placebo controlled double blind comparative studies in chronic urticaria or seasonal and perennial allergic rhinitis patients (PJPR0039, 0067, 0023, 0024, 0054, 0056, 0057) and the placebo controlled long term double blind comparative studies in healthy volunteers (PJR0027, 0031: in other patient studies were protocoled to carry out lab test only before starting treatment and after completion of treatment and weekly incidences of abnormalities during the treatment were not collected) were reviewed. The response stated an increase in the incidence of adverse drug reactions and abnormal lab test values due to a long-term treatment had not been observed so far.

The Evaluation Centre thinks those responses are satisfactory in general, but safety of fexofenadine in long-term use needs to be continually monitored by collecting more safety data and analysing it after the launch.

2) Condition of ECG monitoring and effects of fexofenadine on QTc prolongation

When the applicant originally applied for approval, ECG monitoring was not carried out in Japanese clinical studies in patients. The Evaluation Centre asked the rationale for not

including ECG monitoring in the required test items in the Japanese phase II dose selection studies. Also, it was asked why the applicant declared lack of effects on the QT interval in the Japanese population (especially in elderly patients, patients with liver or kidney impairments).

The applicant's responses were as follows. At the end of year xx when the protocols for the Japanese phase II dose selection studies were prepared, the applicant had the following clinical findings. (1) In the overseas phase I studies, 800mg single dose and 690mg repeated dose twice daily for four weeks demonstrated no effect on ECG. (2) In the overseas comparative study with terfenadine (PJPR0004), QTc prolongation was observed with 60mg and 180mg terfenadine following increases of the terfenadine blood concentration, but patients who received administration of fexofenadine hydrochloride solution at a dose level of 180mg did not show significant changes in QTc. (3) A change in the QTc interval was not observed in the overseas special population studies (PJPR0020 in the healthy elderly population, PJPR0013 in the renally impaired population, PIPR0021 in the hepatically impaired population: all of them received a single dose of an 80mg capsule). (4) When erythromycin or ketoconazol, which were known to increase plasma MDL16,455 (a free-form of fexofenadine hydrochloride without hydrochloride) concentrations, were concomitantly administered in the overseas phase I studies, it was confirmed that fexofenadine did not cause QTc prolongation unlike fexofenadine. (5) In the overseas long-term studies in volunteers (PJPR0027 with 240mg once daily for 12 month, PJPR0031 with 60mg twie dauly for six month), there was no difference in the effect on the QTc interval compared with the placebo group. (6) In the overseas phase III comparative studies (seasonal allergic rhinitis), fexofenadine was administered up to 240mg twice daily and effects on the QTc interval were also investigated. There was no difference from the placebo group. (7) In the Japanese phase I studies, single doses up to 240mg and repeated doses up to 120mg twice daily for one week were investigated. There was no ECG abnormality including QTc prolongation. (8) In the post-marketing adverse drug reaction reports of terfenadine (terfenadine appears as MDL16,455 in plasma but an increase in the concentration of unchanged terfenadine causes QTc prolongation), it was reported that cardiovascular adverse drug reactions such as ventricular arrhythmia occurred when terfenadine was administered to

patients with a risk factor of metabolism impairment in Japan as well as in the overseas countries. Therefore, effects of terfenadine and fexofenadine on ECG were considered to have on racial differences. Based on the above, the applicant judged that it was not necessary to include ECG monitoring in the required test items.

Furthermore, the applicant believed clinical pharmacological investigation on ECG would provide more accurate information than studies in out-patients that measure ECG as a part of safety assessment because ECG has a diurnal variation and requires measurements to be taken at a fixed time before and after administration. They carried out ECG monitoring in the Japanese phase I studies (single dose, yy, to mm, repeated dose mm, yy, to mm, yy). They also decided to investigate ECG in the drug interaction study in Japan and carried out the placebo controlled comparative clinical pharmacological study (J1105) to investigate the effect on ECG when erythromycin was used concomitantly.

The applicant concluded that safety with regard to QTc prolongation in the Japanese patient population including elderly patients, patients with liver impairment and patients with kidney impairment was confirmed by a combined result from; 162 patients in the overseas studies in healthy volunteers, elderly patients and subjects with hepatic or renal function impairment; the Japanese volunteer studies; the erythromycin combination study in Japan to investigate effects on QTc at high blood concentrations; ECG examination in 162 patients in the placebo controlled dose comparison study (J3106) that was implemented as a result of an instruction given by the Evaluation Centre at the first hearing.

The Evaluation Centre believes the “Complete Clinical Data Package” has been completed by the implementation of the study J3106. They considered the claim made by the applicant, i.e., there is no safety issue regarding QTc prolongation by fexofenadine, to be satisfactory in general. However, monitoring of safety of fexofenadine in the special populations, for example, allergic rhinitis and urticaria patients who are elderly or with hepatic or renal impairment needs to be continued in

future by collecting and analysing safety data after launch (refer to "QTc prolongations in elderly").

In an early stage of development, the applicant carried out the development without planning to use the bridging concept in the approval application. Therefore, they investigated QTc only with 40 healthy adult male volunteers in the Japanese single dose study (J001) then the Japanese phase II dose selection study was started on mm, yy. The Japanese clinical pharmacological study with concomitant use of erythromycin (J1105) was implemented later, at yy, - mm.

3) Case reports regarding QTc prolongation and a potential of QTc prolongations in elderly

The original submission document included an article in the Lancet regarding a patient who developed QTc prolongation after fexofenadine administration (353:980, 1999). However, it did not refer to opinions of the doctor and the applicant (Hoechst Marion Roussel) regarding the report (Lancet 353:2072, 1999). The Evaluation Centre questioned this and the applicant responded by adding the detail of the Lancet articles, mounting a follow-up investigation and presenting results of a gene analysis of the patient on several genes that were considered to influencing QTc interval prolongation (carried out with the cooperation of the doctor). The applicant concluded that the prolongation observed in this patient was caused by the underlying condition of the patient. The Evaluation Centre accepted the response.

The Evaluation Centre requested a review of differences in the frequency and the degree of the QTc interval of elderly and non-elderly patients included in the safety analysis of the "Complete Clinical Data Package" by carrying out stratified analysis. The applicant presented results of stratified analysis of elderly patients (65 years old or older) and non-elderly patients (less than 65 years old) in the clinical studies in patients (PJPR0019, 0023, 0024, 0056 and 0057) that were protocoled to perform ECG monitoring before and after administration and included these in the submission (the additional Japanese study was not included). In those studies, the total of one thousand five hundred ninety

nine non-elderly patients and 14 elderly patients received fexofenadine, 519 non-elderly patients and three elderly patients received placebo. Of those 2,121 patients, pre-dose and post-dose QTc values were measured in 1,536 non-elderly patients and 13 elderly patients on fexofenadine, and 494 non-elderly patients and three elderly patients on placebo. The mean changes in the QTc interval ± SD (msec) were –0.20 ± 24.25, 12.67 ± 20.66, 1.09± 25.24 and 13.33±25.17, respectively. In elderly patients, the post-dose ECG in the fexofenadine group and the placebo group showed an average QTc prolongation of 10msec from the pre-dose ECG and there was no difference in the degree of prolongations between groups. The applicant regarded the change as within a range of the physiological change. When comparing the maximum prolongation of the QTc interval, the maximum value was 120msec in non-elderly whereas 42msec in elderly (6x years old, male, 120mg once daily, pre-dose QTc 333msec, post-dose 375msec). The incidence of QTc outliers (patients with post-dose QTc over 440msec and also more than 10sec of prolongation) was 7.7% in elderly (1/13; 6x years old, female, 120mg once daily, pre-dose 410 msec, post-dose 451 msec). The incidence of QTc outliers in the long-term studies in volunteers (PJPR0027 and 0031) was 8.6% (18/209) in the 6-month study and 9.9% (23/233) in the 12-month study, which were higher. The applicant concluded that even though the number of subjects was small, results so far from the elderly population suggested the incidence and the degree of QTc interval prolongation were not higher than non-elderly. The Evaluation Centre accepted this response.

In the original application, ECG monitoring before and after administration in patients was not performed in Japan. In the additionally performed placebo control parallel group dose comparison study (J3106) in seasonal allergic rhinitis patients, ECG monitoring was performed in two centres and it was included in the required test items. Fifty-five patients in the placebo group, 53 patients in the 60mg group and 54 patients in the 120mg group had ECG monitoring. Of those, only one in the placebo group had a deviation from QTc standard value (450msec or over). The incidence of cases who had 30msec or longer prolongations of QTc after administration was 7.3% in placebo group (4/55), 7.5% (4/53) in the 60mg group, 3.7% (2/54) in the 120mg group. (Assessment criteria of abnormalities in QTc interval in Japanese studies were set up according to the Point to Consider in “The assessment of the potential for QT interval prolongation by

non-cardiovascular medicine products, CPMP/986/96, 1997" by CPMP (http://www.eudra.org/humandocs/PDFs/SWP/098696en.pdf/).) In the Japanese studies, only one case, in the 120 group, was over 65 years old. In this patient, ECG monitoring was not performed.

The Evaluation Centre concluded that it was not possible find out the incidence of QTc abnormalities in elderly patients due to insufficient data and further collection of safety information after launch would be required.

3. RESULT FROM A RELIABILITY CHECK BY KIKO AND INTERPRETATION BY THE EVALUATION CENTRE

(1) Interpretation of the reliability check result

The Kiko has carried out an audit on documents as stipulated in the last paragraph of Section 4, Article 14 of the Pharmaceutical Affairs Law. There was incompatibility in some parts (e.g. protocol violations in some clinical study results). However, the Evaluation Centre considered that the audit result would not cause an impediment in carrying out an evaluation based on the submitted approval application.

(2) Interpretation of the GCP inspection result

The GCP inspection did not show a serious deviation from the standard.

4. OVERALL ASSESSMENT BY THE EVALUATION CENTRE

As long as a consultation with the expert committee members does not point out a specific issue, the Evaluation Centre has no objection in approving the filed drug. However, the Evaluation Centre believes appropriate post marketing surveillance is required in order to confirm safety in long-term use and safety in the elderly population.

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After the expert discussion, the following issues were reviewed and appropriate measures have been taken.

D. Data on Acute Toxicity, Subacute Toxicity, Chronic Toxicity, Teratogenicity and Other Toxicity

A narrative of the results of the mice three-month feed-mixed toxicity comparison study xxx in the Gaiyo was amended as appropriate. A narrative regarding AUC of terfenadine and fexofenadine was also added to the Gaiyo.

E. Data on Pharmacological Action

Appropriateness of the claim made by the applicant regarding pharmacological action of fexofenadine was re-examined. The response of the applicant submitted included the following points. An inhibition in release of chemical mediators was observed at a blood level close to Cmax of the clinical dose in the *in vivo* study (guinea-pigs), even though the effect was seen at different concentrations depending on the experimental system. In the overseas clinical studies, improvements in the symptoms of blocked nose, which was believed to involve chemical mediators other than histamine, were observed.

The Evaluation Centre accepted the responses after imposing appropriate amendments in a part of the prescribing information.

F. Data on Absorption, Distribution, Metabolism and Excretion

The applicant was asked to provide comprehensive discussion on the applicant's account that the difference in bioavailability in species was due to the difference in the effect of the first pass. The response of the applicant included the following points. They believed that excretion from the liver was important as a factor affecting the first pass

effect. When the estimated liver extraction rate was used as an index of the first pass effect, it agreed with the fact that rats had especially low bioavailability.

Association of an increase in fexofenadine blood concentration when it was used concomitantly with drugs such as erythromycin and an occurrence of an adverse drug reaction was confirmed. The applicant stated that in an overseas clinical study, even when a dose which was four times higher than the recommended dose (480mg) was administered, there was no difference in occurrence of adverse events or effects on QTc interval compared with the placebo group. Considering this fact and clinical experience abroad (experience in 1.2 billion patient-day worth of prescription), they argued the number of adverse events from combination therapy with erythromycin (16 cases) in the post marketing safety update was low. The Evaluation Centre confirmed the details of adverse events presented and accepted the responses. The Evaluation Centre instructed the applicant to add appropriate narratives in the Precautions for Use regarding increases in fexofenadine blood concentration.

G. Data on Results of Clinical Trials

There was an instruction on the incidence of headache and liver function abnormalities. The applicant replied that incidences and severities of either of the events were similar to those in the placebo groups in the Japanese and overseas clinical studies.

With regard to the efficacy evaluation of chronic urticaria, the Evaluation Centre requested responses on 1) appropriateness of the evaluation method for rashes, 2) differences in the definitions of chronic urticaria in Japan and abroad.

Regarding 1), the applicant gave the following replies. They used the rash score based on “redness” and “swell” because they believed the overseas assessment method with “the number” of rashes was not necessarily appropriate; the primary endpoint (the total score of the rash score (0-3) and the itchiness score (0-8)) gave weight to the itchiness score. The primary endpoint in the overseas studies was the change in the itchiness score. Regarding 2), the applicant suggested there was no difference in the targeted

population because the overall assessment of literature, etc., did not indicate a difference in diagnostic methods. They also believed that there was no difference in the targeted patients despite the slight difference in the Japanese and overseas protocols (Japan: patients who have recurrent symptoms for more than four weeks, the West: patients with recurrent symptoms over three days a week in six weeks) because acute urticaria would be diagnosed using these definitions.

With regard to the dose selection study in allergic rhinitis xxx submitted in the original application, the applicant was asked to provide 1) the reason for lack of dose response in patients with moderate rhinitis, 2) an explanation on appropriateness of the used model to which an items of interaction was added, 3) a rationale for positioning of the study, which did not show dose response, within the bridging.

Regarding 1), they stated that they were unable to find a clear reason for this, even though the range of moves towards the improvement was smaller when the pre-dose value was low and the changes in environment may have had an influence. Regarding 2), they explained that this was stipulated beforehand in the statistical analysis plan and provided the process of investigation into the interaction which took place after the code break. Regarding 3), because of the primary objective of the study, dose response was not demonstrated, they decided bridging would not be successful with this study only. They added the study provided information such as suggestive dose response from sub-group analysis by severity and a similar trend in the overseas studies.

The Evaluation Centre accepted these responses.

The Evaluation Centre believed that the interdemal histamine test on its own could not be used as a bridging study (Evaluation report (1), page 40). The expert discussion concluded that the Evaluation Centre was correct.

The Evaluation Centre instructed the applicant to confirm safety in long-term use and safety in elderly patients in post-marketing surveillance.

From the above evaluation, the Evaluation Centre has no objection in approval of the filed articles. These articles should be discussed by the 1st Committee on Drugs. The drug substance and the drug product are not classified as a poison or a powerful drug. The re-examination period should be six years, as the product is a drug containing a new active ingredient.