11 November 1999

EVALUATION REPORT

[Product name]	Relenza (Generic name: zanamivir)
[Date of application]	2 August 1999 (application for import approval)
[Applicant]	Glaxo Wellcome
[Unit dealing with application]	NIHS Pharmaceuticals and Medical Devices Evaluation Center
[Coordinating Ctte]	Fourth Subcommittee on New Drugs
[Special note]	Priority Evaluation

[Review Result]

Following deliberation by the Pharmaceuticals and Medical Devices Evaluation Center and the Fourth Subcommittee on New Drugs, we believe that in order to bridge between the Japanese and foreign data on zanamivir, there is a need to demonstrate at least the efficacy of the drug in a Japanese clinical study and the communality of the Japanese late Phase II dose finding study and the foreign clinical study data. We consider that the results up to the late Phase II study conducted in Japan have failed to verify the efficacy of this drug and that it is difficult to judge the efficacy of this drug in Japan at the present point in time.

However, as it seems that to the extent that we can evaluate studies conducted in Europe and the southern hemisphere, it would seem that efficacy has been proved in these regions, considering the social necessity for this drug, we have decided to pass the matter to the Special Subcommittee. If the Special Subcommittee concludes that 'Approval of zanamivir is warranted', we believe the approval conditions below must be attached.

[Uses] Infection with influenza virus A or B

[Dosage and administration] The usual adult dose is 10 mg as zanamivir (2 x 5 mg blisters) twice daily for 5 days using a special inhaler.

[Approval conditions]

1) Appropriate postmarketing surveillance must be undertaken to verify the efficacy and safety of zanamivir and interim analysis must be undertaken aiming for 3 years and the results presented without delay to the regulatory authorities.

   The progress of the surveillance must be reported at regular intervals (every six months).

2) Appropriate postmarketing surveillance must be undertaken without delay and the optimum dose of zanamivir for Japan established.

3) The pharmacokinetics of the drug must be established in Japan without delay.

4) Medical workers must provide patients using zanamivir with satisfactory information about the handling of the inhaler including guidance such as by demonstrations using a placebo.

5) As the efficacy of zanamivir in high risk groups in Japan is not yet proven, the definitions and criteria for high risk groups in clinical trials to date must be clarified and a Japanese clinical trial conducted focusing on high risk groups.

6) The findings for clinical trials in high risk patients conducted overseas must be reported to the regulatory authorities as they become available.

7) Results of the ongoing foreign survey on the development of resistance to zanamivir must be reported to the regulatory authorities as they become available.

8) If there is any change overseas in the uses, dosage and method of administration and precautions and warnings, having notified the regulatory authorities without delay, appropriate information must be provided in the field.

10 December 1999
Drug Safety Bureau, Evaluation Division

EVALUATION REPORT (2)

[Product reviewed]	Proprietary name Relenza Generic name: zanamivir
[Date of application]	2 August 1999 (application for import approval)
[Applicant]	Glaxo Wellcome
[Subcommittee]	Standing Subcommittee Review
[Special note]	Priority Evaluation

[Review Result]

The approval of zanamivir is warranted as long as the approval conditions (Draft) are amended as follows.

[Approval conditions]

1) Appropriate postmarketing surveillance to verify the efficacy and safety of zanamivir [including the Japanese postmarketing clinical trial in 2), study to clarify pharmacokinetics in 3) and clinical trial in high risk groups in 5)] must be undertaken over the period of three years from the date of approval (hereinafter called the 'survey period') in order to permit re-evaluation based on the provisions of Article 14, Clause 4-1 of the Pharmaceutical Affairs Law (Act No. 145, 1960) and the results must be submitted to the regulatory authorities within three months calculated from the date when the survey period will have elapsed. Reports on the progress of the surveys must also be presented at regular intervals (every six months).
2) An appropriate postmarketing clinical trial must be undertaken without delay and the optimum dose of zanamivir for Japan established.
3) The pharmacokinetics of zanamivir in Japan must be established in Japan without delay.
4) Medical workers must provide patients using zanamivir with satisfactory information about the handling of the inhaler including guidance such as by demonstrations using a placebo.
5) In order to verify that zanamivir is effective in high risk groups in Japan, the definitions and criteria for high risk groups in clinical trials to date must be clarified and a Japanese clinical trial conducted focusing on high risk groups.

6) The findings for clinical trials in high risk patients conducted overseas must be reported to the regulatory authorities as they become available.

7) Results of the ongoing foreign survey on the development of resistance to zanamivir must be reported to the regulatory authorities as they become available.

8) If there is any change overseas in the uses, dosage and method of administration and precautions and warnings, having notified the regulatory authorities without delay, appropriate information must be provided in the field.

24 August 1999

REVIEW REPORT (1)

Pharmaceuticals and Medical Devices Evaluation Center

1. Product Summary

[Product name]	Relenza
[Generic name]	Zanamivir hydrate
[Date of application]	2 August 1999 (application for import approval)
[Applicant]	Glaxo Wellcome
[Dosage form, content]	Inhaled powder One blister = one product unit Containing zanamivir hydrate as 5 mg zanamivir per blister.
[Uses]	Infection with Influenza A or B
[Dosage and Administration]	Children aged 12 and over and adults usually inhale 10 mg per dose as zanamivir (2 x 5 mg blisters) twice daily using a special inhaler
[Special note]	Priority Evaluation (provisional) Date of US approval: 26 July 1999

2. Outline of submitted data and summary of evaluation by Evaluation Center

i Origin or course of discovery and overseas usage situation

Zanamivir is an anti-influenza virus drug, a derivative of sialic acid (N-acetylneuraminic acid) developed by Glaxo-Wellcome of the UK from 19**. It is believed to suppress the release of virus from host cells by obstructing neuraminidase on the surface of Influenza A and B virus particles. This drug is synthesized from ** starting material whose side chains at position ** and position ** have been modified so as to form ** between positions ** and **.

As the absolute bioavailability of zanamivir taken orally by healthy adults only averaged 2%, nasal spray and inhalation routes were investigated clinically and inhalation was finally selected. Zanamivir aims to reduce the characteristic symptoms of influenza by inhibiting the release of influenza virus on the surface of airway mucosal epithelium cells and ultimately suppressing the proliferation cycle of the influenza virus. As the Influenza C virus has no structural neuraminidase, it is not a target for zanamivir.

Overseas, it was approved in Sweden in February, in the countries of the EC in June and in the USA in July of 1999. The efficacy of the drug versus placebo control has been demonstrated in clinical trials in Europe and in the southern hemisphere but its efficacy has not yet been verified in

the US and Japan. In February this year, the efficacy of zanamivir was rejected by the members of the FDA Antiviral Drug Products Advisory Committee. However, it was held in a later FDA review that that approval had been obtained in the US because ① the clinical trials on zanamivir had been conducted on a world-wide scale, ② that no drug acting on both influenza A and influenza B existed and ③ that the applicant had agreed to report the results of currently ongoing US study (pediatric, prophylactic) conduct a Phase IV postmarketing study.

A homologous drug is amantadine which acts against the influenza A virus, whose mechanism of action is believed mainly to involve obstructing the budding and release of the virus in the early stages of infection.

As the vote by the FDA Advisory Committee in February of this year had been for rejection by 13 to 4, the Evaluation Center is seeking the details of the dealings between the FDA and the applicant following the FDA Advisory Committee meeting and the applicant's interpretation thereof.

ii Data on physicochemical properties and data on specifications and test methods etc.

(Drug substance) Zanamivir is recognized as a ** crystalline form of ** and zanamivir hydrate. Zanamivir hydrate is a non-stoichiometric crystal form and held to contain ** per unit crystal lattice within the crystal lattice. ** zanamivir hydrate obtained by recrystallizing ** from ** is used for the product. Of the related substances derived from the synthesis process possibly incorporated into the drug substance, specifications have been set for **. Whereas zanamivir hydrate is hygroscopic, the moisture content of ** is held to be constant and ** has been set as the reference standard for the quantitation method.

(Product) As the agent is a powder for inhalation, specifications for ** have been set.

The Evaluation Center considered that the hygroscopicity of the drug substance (zanamivir hydrate) could pose a problem in relation to the properties of the product. They asked for the reasons for the selection of the drug substance to be explained and queried whether the identification tests for the drug substance had been set properly. As three types of dosage form had been used in the clinical trials, they asked about the route whereby the 5 mg/blister product had finally been chosen and whether the product design and setting of specifications had been done properly (no response submitted).

iii Data regarding stability

(Drug substance) The results of stress tests on the drug substance indicated changes in ** to humidity and light and ** was noted to temperature and humidity. In accelerated tests and long term storage tests (30°C, 60% RH, shaded from light) on the hermetically-sealed final packaged form, it was judged that no changes over time had been noted. The storage method was thus set as 'Storage conditions: Protect from light. Container: Airtight' and no expiration period was set.

(Product) As the product is packed in aluminium blisters, no changes were noted even under the heating conditions (**) in the stress tests and as no changes over time were noted in the accelerated and long-term storage tests either, it was judged that quality would be maintained for three years at least and no expiration period and storage method were set.

The Evaluation Center asked whether it was valid to set ** as ** material had been found in the long term study on the drug substance (no response submitted).

iv Data regarding acute toxicity (single dose), subacute and chronic toxicity (multiple dose), teratology (reproductive and developmental toxicity) and other forms of toxicity

Data on an acute (single dose) toxicity study, subacute and chronic (multiple dose) toxicity study, reproductive and developmental toxicity study, antigenicity study, mutagenicity study and oncogenicity study were submitted as toxicity studies.

The routes of administration used in the single and multiple dose toxicity studies were spray inhalation using the liquid and powder and intravenous administration. For the reproductive and developmental toxicity study, intravenous injection was used instead of inhalation, for the antigenicity study intraperitoneal and subcutaneous routes were used and spray inhalation of the powder was used in the oncogenicity study.

The approximate lethal dose to rats by inhalation in the single dose toxicity study was 49.7 mg/kg or over in males and 56.3 mg/kg or over in females due to the maximum dose which could be administered and to dogs was 28.4 mg/kg or over, which was the maximum dose which could be administered. The approximate lethal dose to rats by intravenous injection was 90 mg/kg or over,

which was the maximum dose which could be administered and in dogs was 36 mg/kg and over due to the maximum dose which could be administered.

The non-toxic dose levels to rats were judged from the 1-month inhalation study, 1-month intravenous study and 6-month inhalation study to be respectively 37.1 mg/kg/day, 90 mg/kg/day and 44.5 mg/kg/day. The non-toxic dose levels to dogs were judged from the 1-month inhalation study, 1-month intravenous study and 6-month inhalation study to be respectively 8.7 mg/kg/day, 36 mg/kg/day and 10.5 mg/kg/day.

'Reddening of the ears or gums' was found in the various studies. Gasping and congestion of the lungs were seen in the rat 1-month inhalation study, and alveolar macrophage infiltration in the 6-month inhalation study. Vomited material was observed in the dog 8-day inhalation study and soft feces in the 1-month intravenous study. Histopathological examination in the dog 6-month inhalation study revealed fibrosis and inflammation of the bronchial lumen.

In the foetal organogenesis study in the reproductive and developmental toxicity studies, teratology was found in rats and rabbits. The mean plasma concentrations of the drug in the perinatal and lactation study were lower than in the fertility and general reproductive toxicity study or organogenesis study.

No antigenicity due to zanamivir was noted in the antigenicity study using guinea pigs.
The results of the mutagenicity study with zanamivir were negative and it was also judged not to be oncogenic in a study using rats and mice.

As an upper specification limit for impurities in the drug had been determined, safety was judged not to be a problem within the specification range and no toxicity study on them was undertaken.

As zanamivir is excreted rapidly from the kidneys following administration, the toxicity of metabolites was not investigated.

The Evaluation Center is seeking clarification from the applicant regarding the following points (responses not submitted).

Re: The toxicity studies overall

* The spray inhalation tests in the inhalation study were conducted using liquid and powder agents. Why were different preparations used?
* Were no abnormalities in respiratory condition due to administration of the drug seen?
* Was there no relationship between the degree and frequency of the 'reddening of the ears and gums' and dose in the various studies.

Re: Single dose and multiple dose toxicity studies

* The validity of using one control group animal in place of a test animal which died in the rat intravenous study.
* Was not there the vomiting seen in the dog 8-day inhalation study an effect of the drug? Moreover, was it confirmed that no drug had been detected in the plasma in the non-dosed and vehicle-dosed animals.
* Were not the gasping and congestion of the lungs seen in the rat 1-month inhalation study effects of the drug? Further, amongst the high dose females, an animal was killed in extremis on the first day following completion of dosing due to gasping and pallor of the extremities. What were the reasons for not using this case as evidence for estimating the non-toxic dose. Give a detailed explanation of why the increase in MCV was held to be of little toxicological significance.
* Soft feces were observed in the dog 1-month intravenous study. Were the degree and frequency thereof correlated to the dose?
* Explain the mechanism of alveolar macrophage infiltration seen in the rat 6-month inhalation study.
* Explain any dose correlation whilst demonstrating the results for each lobe for the bronchial lumen fibrosis and inflammation seen in the histopathological investigations in the dog 6-month inhalation study.

Re: Reproductive and developmental toxicity studies

* In the tests to check the effects on behavioral function seen in F1 males in the fertility and general reproduction studies, give the reasons why, whereas dosing continued throughout the lactation period in the former, the dosing period was the gestation period in the latter.
* Explain in detail the rat and rabbit teratology seen in the fetal organogenesis study.

* Give the reasons why mean plasma concentrations in the perinatal and lactation study were lower than in the fertility and general reproduction studies or the organogenesis study.

Others

* Give details of the pale foci seen in the lungs during the rat 104-week carcinogenicity study

v Data regarding pharmacology

The intracellular transfer of zanamivir is not more than 1% and it is inferred mainly to act in an extracellular fashion. Its mechanism of action is held to involve suppressing neuraminidase in the influenza virus (A and B) to obstruct the release process outside the cell for virus which has multiplied inside the cell and so suppress the influenza virus proliferation cycle.

Its *in vitro* inhibitory action towards the neuraminidase activity of Influenza A and B viruses was investigated taking 2'-(4-methylumbelliferyl)-α-D-N-acetylneuraminic acid as the substrate and the IC_{50} of zanamivir in Japanese and foreign clinical isolates was 0.0003~0.01 μ,l. Moreover, whereas its *ki* value to various types of neuraminidase was respectively 10^{-9} and 10^{-8} ,l for influenza virus A and B, with human placenta-derived neuraminidase and *C. perfringens* derived neuraminidase, it was respectively about 10^{-3} and $>10^{-4}$,l. In plaque formation and virus release tests in MDCK (Madin Darby canine kidney) cell and human respiratory organ epithelial cell hosts, zanamivir exhibited concentration-dependent inhibitory activity and the IC_{90} thereof was lower than for amantadine and rimantadine except in a few cases. It was also shown to inhibit plaque formation by amantadine-resistant clinical isolates of Influenza A (IC_{90} 0.24-80 μM).

In animal models of *in vivo* infection, mainly ferrets (4-5 per group) and mice (4 per group) were used. The dosing method was mainly nasal instillation and there was only one study by inhalation. Having inoculated the mice with the virus, nasal instillation of the drug twice daily for three days reduced the level of virus in the lungs dose-dependently on days 1-3 following inoculation. When virus-infected ferrets had the drug instilled nasally twice daily for five days, the level of virus in nasal cavity washings was reduced on days 1-9 following inoculation and no fever was found in the 0.75 mg/kg group. In virus-infected ferrets, the group dosed with zanamivir 26 hours and 2 hours prior to inoculation showed lower virus titers in the nasal cavity washings than the group dosed 5 or 22 hours after inoculation and as this action was dose dependent, it was suggested that it was desirable for administration of the drug to commence as early as possible after infection.

Moreover, in the influenza B resistant strain found in one case in the clinical studies, it was shown that mutation had occurred at one position in the amino acid sequence of neuraminidase.

The Evaluation Center is asking for responses about the validity of selecting mainly ferrets as the experimental animals in the *in vivo* studies and MDCK as the host cells and the validity of conducting most of the study by nasal instillation despite the fact that the actual method of clinical use is oral inhalation. They queried the disparity in IC_{50} for inhibitory activity against plaque formation and for suppression of neuraminidase and have asked for discussion of this. As a cause of this, the Evaluation Center wonders whether, because the substrate used for the determination of neuraminidase activity used in the *in vitro* experiments was a monosaccharide derivative, competitive inhibition of the drug and substrate would be easier to detect than with the complex sugar chains forming *in vivo* substrates, and requested the submission of any literature surveying the inhibitory action of zanamivir taking complex sugar chains, glycolipids or disaccharides as substrates. They also are having the reasons for the high affinity of zanamivir to influenza virus neuraminidase considered.

As zanamivir acts extracellularly, answers are being sought as to how it is thought to reach the active site after being inhaled and also the extracellular concentrations anticipated.

The Evaluation Center is examining whether the reasons why the efficacy of zanamivir was not verified in the Japanese and US clinical studies despite the potent anti-neuraminidase activity of the drug can be explained from *in vitro* and *in vivo* studies.

Action on water and electrolyte metabolism was noted in relation to the general pharmacology study results on zanamivir and as decreases in serum sodium had been noted in the dog 1-month study in the toxicity studies, discussion about the correlations of these are being sought. Moreover, they are in the process of checking whether there are any data on the pharmacological activity and general pharmacological activity of impurities at the time of synthesis. Many points are still unclear at the current scientific level as regards whether the ligands can recognize the receptor sugar chains. They are checking whether there are any data concerning the effects of zanamivir on ligand-receptor interactions even if structural similarity between the drug and ligands is poor.

vi Data regarding absorption, distribution, metabolism and excretion

In order to determine the pharmacokinetic parameters of the drug, rats and dogs were dosed intravenously, orally or by tracheal instillation with [^{14}C]-zanamivir at a concentration of 10 mg/kg unless otherwise stated.

The half life ($t_{1/2}$) of a single intravenous dose of zanamivir to male rats and male dogs was approximately 0.6 hour for radioactivity and 0.3 hour for the intact compound in rats and approximately 0.8 hour for radioactivity and 0.8 hour for the intact compound in dogs. With the administration of multiple doses of the drug to rats and dogs, AUC on day 1 of dosing rose dose-dependently and a straight line passing virtually through the origin was found between dose and AUC, confirming linearity. No marked increases in the AUC of plasma zanamivir or decreases in creatinine clearance were found on day 35 of dosing in rats and day 22 of dosing in dogs.

As regards distribution, no high concentrations or residues of zanamivir were noted in particular tissues. The transfer of zanamivir in the placenta and fetuses of pregnant rats was found as relatively high levels of radioactivity in the reproductive organs of the uterus, ovaries and placenta on days 12 and 18 of gestation. However, the concentrations were lower than in the blood and radioactivity in the fetuses was held to be low. The drug was shown not to be metabolized in the liver but to be excreted mainly as the intact compound from the kidneys.

The pharmacokinetics in man were investigated by administering a single inhaled dose of 5mg, 10mg and 20mg zanamivir to six fasting healthy Japanese adult males. With administration of 10 mg, Tmax was 1.6 ± 0.5hr, Cmax 40.8 ± 12.5ng/mL, t1/2 2.8 ± 0.8hr and $AUC_{0-‡}$ 211.1 ± 57.2ng.hr/mL. As against this, the administration of 10 mg overseas produced Tmax of 1 ± 1hr, Cmax of 95 ± 34ng/mL, $t_{1/2}$ of 4.59 ± 2.48hr and $AUC_{0-‡}$ of 655 ± 365ng.hr/mL. With the administration of multiple inhaled doses of 20 mg twice daily for six days in Japan Cmax and AUC_{0-12} (on day 6 of dosing) were respectively 51.56 ± 17.87ng/mL and 281.6 ± 80.4ng.hr/mL.

Distribution within the lungs upon giving a single inhaled dose of 10 mg zanamivir labelled with ^{99m}Tc has been investigated overseas and deposition in the buccal cavity and throat was 77.6% and

in the interior of the lungs about 13%. The residue in the device or blister was about 8%. The absolute bioavailability of the drug was shown to average 2% (1-5%) overseas.

Investigations in the elderly and adults with diminished renal function have been conducted overseas and Cmax was shown to rise and $AUC_{0-‡}$ to increase but the applicant judges that there is no need for dose adjustment in the majority of cases.

Population pharmacokinetic analysis was also undertaken as investigations in patients infected with influenza and it was shown that the pharmacokinetic parameters in the patients were similar to those in healthy adults. The pharmacokinetic parameters in children were also similar to those in healthy adults.

The Evaluation Center is checking ① whether there are any ADME data for Japanese elderly and child subjects and ② data on the bioequivalence of nasal instillation and inhalation.

Upon comparing the Japanese and foreign pharmacokinetic parameters in man, $t_{1/2}$ and AUC in Japan following a single 10 mg inhalation dose were about one half the levels seen overseas and even when the single dose was increased to 20 mg, $AUC_{0-‡}$ rose only to 508.5 ± 83.1ng.hr/mL. In view of this, the Evaluation Center believes that the possibility cannot be ruled out that inhalation by the diskhaler is inadequate and that most of the drug is absorbed from the gut and not in the lungs. No problems were found with the methods of determination used in the pharmacokinetic investigations and the validation of the detection limits and determination methods.

We believe that investigation by the Subcommittee will be needed as to whether these judgements by the Evaluation Center are valid.

vii Data regarding clinical study findings

As inhalation onto the airway surface where the influenza virus is considered to multiply would seem appropriate for the route of administration for zanamivir in view of its mechanism of action, clinical trials were conducted inferring that oral inhalation on its own or combined oral inhalation and nasal spray would be appropriate.

Tolerability was demonstrated overseas with nasal spray administration at 96 mg/day (16 mg per dose, six times daily) for 5 days and inhalation at 64 mg/day (16 mg per dose, four times daily) for 7 days.

In the Japanese Phase I study, tolerability was demonstrated with inhalation of 20 mg twice daily for six days.

Phase I and II clinical studies have been conducted in Japan but not Phase III. The foreign clinical studies conducted are a clinical pharmacology study in the US and Phase II and Phase III studies in Europe, North America and the southern hemisphere.

[Foreign clinical pharmacology study]

Overseas, a double blind study between zanamivir and placebo in which healthy adults were inoculated with Influenza A and B in the nasal cavity was conducted from ** (month) 19** with the aim of surveying the prophylactic effect of the drug (administration 4 hours before virus inoculation), the efficacy of early therapy (administration 26 or 32 hours following virus inoculation) and the efficacy of late therapy (administration 50 hours following virus inoculation).

In the Influenza A inoculation study, intranasal administration, 3.6-16 mg of zanamivir was administered intranasally twice or six times daily and virus proliferation and the frequency of fever were measured as primary endpoints. Amongst the 16 cases in the prophylaxis group, administration of zanamivir for five days gave 96% suppression of virus proliferation and 95% suppression of fever compared to the 33 cases in the placebo group. In the therapeutic administration study, administration of zanamivir for four days achieved 84% suppression of fever in the 31 cases treated early on compared to the 26 placebo group cases. However, no significant difference from placebo was noted in the group with late initiation of treatment. Twice daily administration of zanamivir significantly reduced virus levels in the same way as six doses daily.

In the prophylaxis study with the Influenza B virus, 3.2 mg per dose of zanamivir was given twice daily or 6.4 mg once or twice daily for five days intranasally. The drug suppressed virus proliferation 50-76% compared to the placebo group and upper airway symptoms due to influenza were 56-62% inhibited in the twice daily dosage group, but no clear therapeutic efficacy was

evident in the group dosed once daily. In the therapeutic administration study, a total of 7 doses of zanamivir was given twice daily from 32 hours after inoculation but no significant difference in therapeutic efficacy was seen between the 10 cases of placebo group and 22 of the zanamivir group. From the results of these studies, it was decided to administer zanamivir twice daily within 48 hours of onset in the Phase II clinical trials. In another study in 13 cases of bronchial asthma, zanamivir had no significant effect on pulmonary function and airway hypersensitivity and in an inhalation study in 138 healthy subjects inoculated with influenza vaccine, the acquisition of influenza antibodies due to the vaccination was unaffected.

[Foreign Phase II studies] (see attached table)

Foreign Phase II studies were conducted in Europe, North America and the southern hemisphere with placebo control giving 10mg by inhalation twice daily for five days and combining 6.4 mg nasal spray and inhalation twice daily for five days. They targeted subjects aged 18 and over in Europe and 13 and over in North America and the southern hemisphere and the evaluation of efficacy in each study included subjects with a total of three or more symptoms comprising the fever which is the characteristic systemic symptoms of influenza plus at least two symptoms from headache, myalgia, cough and sore throat. The rapidity with which these were alleviated was then taken as the primary endpoint. The occasional use of antipyretics and antitussives (excluding anti-tussives in the southern hemisphere) was permitted in each study only if the symptoms were severe.

Analyzing efficacy from the combined European and North American data had been decided on before removing the blinding and multiple analysis was undertaken.

The time to alleviation of the major symptoms of influenza which formed the primary endpoint in the European study was 5.2 days for the zanamivir inhalation group and 5.4 days for the inhalation and intranasal administration group. Both were one day shorter than the 6.2 days in the placebo group but there was no statistically significant difference.

In the North American study, the major symptoms of influenza tended to lessen more quickly with zanamivir than with placebo but there was no statistically significant difference. The number of days (median) to the alleviation of the main five symptoms of influenza in the influenza virus-positive cases

was 5.5 days with zanamivir inhalation, 5.0 days with combined inhalation and nasal spray and 6.1 days with placebo and no statistically significant difference was found.

In the composite analysis of the European and North American studies, the major symptoms of influenza tended to lessen sooner in the zanamivir group but there was no statistically significant difference.

In the southern hemisphere study, the protocol for the evaluation criteria was the same as for Europe and North America but before removing the blinding, they had been altered so that the proportion of patients whose influenza symptoms had been alleviated by day 4 was taken to be the indicator of therapeutic efficacy. The alleviation of influenza symptoms in the zanamivir groups was significant compared to the placebo for both inhalation and combined inhalation and intranasal administration and this trend was pronounced in influenza virus-positive cases.

In the three studies in Europe, North America and the southern hemisphere, no potentiation of therapeutic efficacy was proved with combined inhalation and intranasal administration compared to inhalation on its own.

It was suggested from the above results that the clinically recommended dose of zanamivir for influenza infections would be inhalation of 10mg twice daily for five days.

[Japanese Phase II study] (see attached table)

An Japanese early Phase II study was conducted in patients aged 16-65 years from ** (month) 19**. It looked at patients with a total of three or more symptoms comprising fever of 37.5°C and over plus at least two symptoms from headache, myalgia, cough and sore throat. In principle, treatment was to be started within 24 hours of onset and at the latest within 36 hours and a group combining inhalation of 10mg twice daily for five days with 6.4mg by nasal spray twice daily for five days and a group treated by inhalation only were compared with a placebo group. The concomitant use of antipyretic analgesics and antitussives was prohibited but acetaminophen could be used when necessary only if the symptoms were severe. Efficacy was evaluated taking the rapidity with which the three symptoms of fever, headache and myalgia and the five symptoms of these plus cough and sore throat were alleviated, assessing symptom alleviation to be if body temperature was less than 37.0°C, if the other symptoms were hardly noticeable or if a symptom-free state continued for 24

hours. In the Japanese early Phase II study, the degree of the individual symptoms was classed as one of four grades from none to severe and the subjects recorded the degree of their symptoms on a record card.

There were 87 of the 116 cases included in the efficacy evaluation (per protocol cases) and in the 3-symptom comparison, both the per protocol and ITT analysis indicated median values for symptom alleviation of 3 days in the zanamivir group, significantly less than the 4 days for the placebo group. The median value for the zanamivir group in the influenza virus-positive cases was 3.5 days and no significant difference was noted.

In the 5-symptom comparison, no significant difference was found between the placebo and zanamivir groups.

The late Phase II study from ** (mth) 19** to ** (mth) 19** in cases aged from 16 years compared the inhalation of 10 mg twice daily for five days and 20 mg twice daily for five days taking the same selection criteria as in the early Phase II study. Apart from acetaminophen when required, concomitant therapy of oral antibiotics could be used only if there was a risk of bacterial infection complications. The protocol compatible set comprised 244 of the 318 cases with an influenza positive population of 225 cases (most influenza A, 7 influenza B) and 4 cases were either started on treatment later than 36 hours or an unknown time after onset.

In the major 3-symptom and 5-symptom evaluations, the shortening in the symptom alleviation time by zanamivir was not significant compared to placebo irrespective of whether or not there was positive virus identification or the number of inhalations.

The late Phase II study 2 was conducted from ** (mth) 19** but because a change in the dosage form was investigated, it was stopped at the point when 49 cases had been enrolled even though the target number for the study had been 300 cases. No significant difference was found in the 5-symptom evaluation.

[Foreign Phase III studies] (See attached table)

The foreign Phase III studies were conducted comparing 10mg twice daily for five days by inhalation with placebo. These studies looked at cases aged 12 and over and acetaminophen and antitussives could be used concomitantly only if the symptoms were severe. Cases aged 65 and over or with chronic respiratory or circulatory disease were taken as a high risk group. The southern hemisphere study looked at cases with fever of 37.8°C and over (and/or fever sensations) and at least two symptoms from the four of headache, myalgia, cough and sore throat and treatment with zanamivir was initiated within 36 hours of the onset of influenza symptoms. The usefulness of zanamivir was investigated by comparing the time until fever, headache, myalgia, cough and sore throat were alleviated based on subject evaluation and recording in accordance with a 4-point scale. Alleviation was taken to mean body temperature of less than 37.8°C, absence of fever sensations, and the disappearance or becoming mild of headache, myalgia, cough and sore throat for 24 hours. There were 228 cases in the placebo group and 227 in the zanamivir group and about 70% in each group were influenza-positive (of whom type A accounted for 67% and type B 33%). The high risk group accounted for about 17% of each group, of whom 75% had respiratory disease.

The median time for the alleviation of the five major symptoms was significantly shorter in the zanamivir group at 5 days than in the placebo group at 6.5 days (95% confidence interval for difference between placebo and zanamivir groups 0.5-2.25 days). In the influenza-positive population too, the symptoms lessened significantly more quickly with zanamivir. Between the high risk groups, the symptoms lessened significantly more quickly with zanamivir but no significant difference was noted in the influenza-positive population. The median value for the time until the influenza symptoms lessened and relief medication became unnecessary showed no significant difference at 9 days in the placebo group and 7 in the zanamivir group. The number of days taken for the individual symptoms to be alleviated was significantly shorter in the zanamivir groups for fever sensations and feelings of weakness.

The European study looked at cases with fever symptoms (37.8°C and over, 37.2°C and over if aged 65 or more) and at least two from the four symptoms of headache, muscle or joint pain, cough and sore throat and treatment with zanamivir was initiated on day 1 or day 2 following the onset of influenza symptoms. The usefulness of zanamivir was investigated by comparing the time until the fever, headache, muscle or joint pain, cough or sore throat was alleviated with the placebo group. Alleviation was taken to mean absence of fever (body temperature less than 37.8°C, less than

37.2°C if aged 65 or more) and the disappearance or becoming mild of headache, myalgia, cough and sore throat for 24 hours. There were 182 cases in the placebo group and 174 in the zanamivir group and about 78% in each group were influenza-positive (of whom type A accounted for 95.7 % and type B 4.3%). The high risk group accounted for about 9% of each group, of whom 56% had respiratory disease.

The median time for the alleviation of the five major symptoms was significantly shorter in the zanamivir group at 5 days than in the placebo group at 7.5 days (95% confidence interval for difference between placebo and zanamivir groups 0.75-3.5 days). In the influenza-positive population too, the symptoms likewise lessened significantly more quickly with zanamivir. In the high risk patients, no significant difference was found between the two groups for the rapidity with which the symptoms were alleviated. The median time until the influenza symptoms lessened and relief medication became unnecessary was significantly faster with zanamivir at 5.5 days than with placebo at 8.25. The number of days taken for the individual symptoms to be alleviated was significantly shorter in the zanamivir groups for fever sensations, myalgia or arthralgia, cough and feelings of weakness.

The North American study was conducted in the same target population and with the same efficacy evaluation method as in the European study. There were 365 cases in the placebo group and 412 in the zanamivir group and about 73% in each were influenza-positive (of whom type A accounted for 98% and type B 2%). The high risk group accounted for about 14% in each group.

There was no significant difference between the two groups in median time for the alleviation of the five major symptoms which was 6 days with placebo and 5 days with zanamivir. No significant difference was found between the two groups for the influenza-positive population and high risk patients. No significant difference was found either in the median time until the influenza symptoms lessened and relief medication became unnecessary, at 8 days with placebo and 7 days with zanamivir. The number of days taken for the individual symptoms to be alleviated was significantly shorter in the zanamivir group for cough.

In the above three studies, the therapeutic method, target subjects, evaluation of efficacy and study duration had been about the same. The usefulness of zanamivir was demonstrated in the southern

hemisphere and European studies but no usefulness was demonstrated in the North American study which had a large number of cases. No clear usefulness was demonstrated in the high risk group either.

In the Japanese Phase II studies and foreign Phase III studies, nothing had been specified about the use or otherwise of influenza vaccine and the proportion of cases who had been vaccinated was 6% in the southern hemisphere, 4% in Europe and 14% in North America. The effects of vaccination on the efficacy of zanamivir were investigated in North America where there was a high vaccination rate but no effects were found.

[Safety]

Adverse reactions were noted as 34 episodes in 28 cases out of 291 included in the safety analysis in the Japanese early and late Phase II studies, the principal symptoms being diarrhea 3 episodes, hoarseness 3 episodes, headache 3 episodes, nausea 2 episodes, palpitations 2 episodes and sweating 2 episodes. Similar adverse reaction were found in the placebo group as well, with an incidence of 20 episodes in 13 out of 149 cases. Three cases taking 20 mg zanamivir by inhalation withdrew due to adverse reactions.

Abnormal variations in laboratory tests in the Japanese studies were seen as 41 episodes in 24 out of 280 cases used in the laboratory test survey, with high frequencies for elevation in s-GPT, s-GOT and γ-GTP. In the placebo group, they were noted as 40 episodes in 20 out of 142 cases and high frequency was found for the same items as in the zanamivir group.

Adverse reactions overseas were tabulated separately as during and after treatment. The incidence of adverse events in the zanamivir inhalation group was 395/1132 (34.9%) during treatment and 269/1132 (23.8%) after treatment, the principal ones being the typical symptoms and signs of influenza. Those deemed to be drug-related were 140 cases during and 23 after treatment. Adverse events due to placebo were found in 577/1520 cases during and 363/1520 after treatment and those judged by the Investigators to be drug-related were found in 173 cases during and 23 after treatment. No characteristic adverse events were found in the high risk group, by sex, age, race and the elderly. Serious adverse events caused by zanamivir were one case of treatment withdrawal due to frontal pain and dizziness during treatment, and amongst the two deaths, one elderly patient died of pneumonia and dehydration but was judged by the investigator not to be drug related. Abnormal variations in laboratory tests in the foreign studies were investigated in 2289

cases and those with a frequency of 1.5% and over were HCO_3, calcium, GGT, blood sugar, potassium, s-GOT, s-GPT, hematocrit, neutrophils and white blood cells. No serious abnormal variations were found amongst these and they were held to be variations associated with influenza.

Adverse reactions and abnormal variations in laboratory values were manifested to the same degree in both the zanamivir and placebo groups both Japan and overseas and no serious adverse reactions considered to be caused by the drug.

No acquisition of resistance to zanamivir by the influenza virus was found in the clinical studies. However, a resistant strain of influenza B virus was detected in an 18 month old child following bone marrow transplantation for juvenile chronic myeloid leukaemia with compromised immunity who had been treated with zanamivir on compassionate grounds (Gubareva LV et al. *J Infect.Dis* 178;1257,1998). This patient had been started on zanamivir on day 6 after presenting with influenza but because the virus was still detected even after being treated continuously for two weeks, the drug was withdrawn. The child died two days later. Mutation of the neuraminidase gene was detected in the virus isolated from this patient and its *in vitro* susceptibility had fallen to 1/1000.

The Evaluation Center considers that the Japanese Phase II comparative study findings and North American Phase III comparative study have not gone so far as to verify the efficacy of zanamivir. In order to consider the reasons for this, they sought explanation of the following points from the applicant (responses not submitted).

[Clinical ranking of zanamivir}

In the clinical study findings submitted, it was shown that recovery from the clinical symptoms of influenza took about 1-2 days less with zanamivir. In the Japanese therapeutic scene, cold symptoms can be treated relatively easily with antipyretic analgesics, antitussives and antibiotics etc and many cold drugs are marketed as general medication. In view of the fact that these are used widely before attending clinics, there was a risk that the usefulness of zanamivir might be masked. The Evaluation Center asked for the grounds for asserting that a shortening of influenza symptoms by 1-2 days by zanamivir was clinically significant.

[Foreign clinical studies]

Amongst the three Phase III studies, zanamivir had been shown to be effective in the southern hemisphere and European studies but not in the study conducted in North America. The applicant stresses that zanamivir is useful because when a proportional odds model was applied to evaluate interactions in terms of efficacy between these three foreign studies, interaction was no statistically significant at a significance level of 5% and they judged that an analysis combining the three studies would be possible, and that zanamivir was demonstrated to be effective when this analysis was done. However, no efficacy was demonstrated in the North American Phase III comparative study which had the largest sample size (n=777) and the Evaluation Center judges that because efficacy was not demonstrated in the Phase III studies conducted with smaller samples in the southern hemisphere (n=455) and Europe (n=356), doubt remains as the external validity regarding the efficacy of zanamivir and believes that the features and usefulness of this drug have not been clearly shown from the data submitted.

In the foreign Phase III studies, the therapeutic efficacy of zanamivir was investigating defining a high risk group comprising the elderly aged 65 and over or those with chronic respiratory or cardiovascular disease but the proportion of high risk cases in these studies was only 9-17% and most of these patients were relatively young bronchial asthmatics (median age 44.2-57.0 years; 70% approx). The applicant asserts that the setting of the high risk group in the foreign clinical studies was appropriate because it complied with the definition of high risk group in the advice on influenza vaccination from the US prophylactic vaccination advisory committee (April 1999). A reply was received to the effect that a therapeutic study in high risk groups is also currently ongoing in the northern hemisphere and there are plans to evaluate efficacy in high risk patients. Accordingly, the Evaluation Center judges that the efficacy of zanamivir in high risk groups has not yet been clearly demonstrated from the data submitted.

The Evaluation Center enquired why the subgroup analysis in the Phase III studies had produced inverted results for therapeutic efficacy (in the North American study, symptom recovery in the placebo group had been superior to the zanamivir group in the high risk influenza-positive population and influenza-positive non-white population). The reply received was that it seemed the small number of target subjects in each sub group had caused the inversion of therapeutic efficacy and that because the safety investigations in each subgroup indicated conformity of results with the

cohort as a whole, this posed no particular problem to the interpretation of the study results. The Evaluation Center accepted this.

[Japanese clinical studies]

In the early and late Phase II studies conducted in Japan, the rapidity of influenza symptom improvement which formed the primary endpoint compared with placebo fails to prove the efficacy of zanamivir. The Evaluation Center further enquired about clinical studies planned by the applicant for this winter season in order to press on with the review when there are no data verifying the efficacy of zanamivir in Japan at the present time. The applicant replied that they plan to conduct a prophylactic administration study on zanamivir in the elderly aged 65 and over and health workers but have no plans for further studies on therapeutic administration as in the Phase II study. They believe that the efficacy of zanamivir has been satisfactorily demonstrated by the foreign Phase III and Japanese Phase II studies submitted as application data.

Three influenza symptoms were evaluated as the primary endpoint for efficacy in the Japanese Phase II study and five symptoms were evaluated as the primary endpoint overseas. The validity of setting only three symptoms as the primary endpoint in Japan was queried.

[Timing of zanamivir administration and method of treatment withdrawal]

Therapeutic efficacy was obtained by starting treatment within 48 hours of the onset of influenza symptoms in the clinical study results submitted. However, it would seem to take some time for patients to acquire the proper method of inhalation of the drug using the diskhaler and it was queried whether any delay in becoming accustomed to the inhalation technique could possibly disrupt the timing of the therapy (in particular, it would seem to take a long time for the elderly to acquire the technique). The applicant was also asked how they planned to deal with patient guidance on the inhalation method not only as regards the method of inhalation with the inhaler but including information on fitting the rotadisc into the inhaler (those with 4 blisters contained in the disc).

Despite the fact that it had been imagined that therapeutic efficacy would be potentiated by combining nasal administration with inhalation in view of the mechanism of action of zanamivir, it had not been proved in the foreign Phase II studies that the clinical efficacy of combined intranasal

administration and inhalation was superior to inhalation on its own. The reasons for this were asked about.

[Safety]

It has been concluded that no significant difference was found between the placebo and zanamivir groups in the frequency of adverse events in the Japanese and foreign comparative studies and that the safety of the drug had been assured. There would seem to be a possibility that because the placebo group had inhaled a powder containing lactose, adverse events had been induced in this group due to the inhalation of this powder. There was therefore feared to be a possibility that the placebo group had not been appropriate in terms of looking at safety and that the difference in the frequency of adverse events compared to the zanamivir group had been indistinct. The Evaluation Center sought an explanation from the applicant on this point.

When they also asked about the applicant's monitoring plans for resistant influenza viruses (surveillance) due to the fear of the appearance of resistant strains if zanamivir were to be used widely following its commercial launch, the applicant replied that with the co-operation of public bodies such as the WHO (World Health Organization) and CDC (US Communicable Disease Center), they would set up a surveillance network for neuraminidase inhibitor susceptibility. They then planned to establish a committee made up of influenza specialists from the public bodies and the applicant to standardize the monitoring procedures and undertake this surveillance over 4 to 5 years and furthermore to set up a data base with all the information obtained from the specimens at the test centers. The Evaluation Center accepted this.

[Validity of dose and administration, precautions and warnings]

Supposing zanamivir were to be approved at the present time, the Evaluation Center believes there is a need to make clear in the Precautions and Warnings (draft) that the Japanese and North American clinical studies have not gone so far as to verify the efficacy of the drug.

They also are seeking clarification from the applicant about the need to include the following points in the Precautions and Warnings (draft) (no response submitted).

* The validity of having cases aged 12 and over as subjects in the Japanese study despite the fact that cases less than 16 have not been

* The need to state that pharmacokinetics in hepatically impaired patients have not been investigated and that safety in patients with severe renal compromise is not proven

* Because usefulness is not proven if treatment is initiated more than 48 hours after the onset of influenza symptoms, the need to state this in the Precautions and Warnings

* As there is also a possibility of bronchoconstriction being caused by zanamivir in patients with bronchial asthma or chronic obstructive pulmonary disease, the need to state that "zanamivir should be administered with care and if any bronchoconstriction occurs, treatment with inhaled bronchodilators etc. is to be given".

* The need to state that there is no proof in Japan of the efficacy of zanamivir used as prophylaxis for influenza

* Because as regards use in pregnancy, there is no experience of its use in Japan and it is judged that safety has not been proven, the need to restrict the use of zanamivir in pregnancy.

The Evaluation Center believes furthermore that as with amantadine, the 'Precautions and Warnings relating to potency' need to state ① that zanamivir must be administered only if judged particularly to be necessary by a physician, ② that consideration should be given to the fact that zanamivir is a supplement to vaccine therapy and ③ that zanamivir is not effective against influenza C.

We believe that the Subcommittee needs to examine whether or not these judgements of the Evaluation Center are valid.

3. Overall evaluation of Evaluation Center

From the data submitted and following the investigations outlined above, the Evaluation Center judges that the *in vitro* efficacy of zanamivir has been verified biologically and pharmacologically but that the clinical studies, whilst verifying efficacy in Europe and the southern hemisphere, have failed to do so in the US and Japan. It would thus be difficult to say that the efficacy of zanamivir has been satisfactorily confirmed at the present point in time

In order for this drug to be approved in Japan, we believe that ultimately the findings of a Phase III study in Japan will need to be confirmed. If there is a need for early approval in view of urgent

public health consideration (demand from the authorities), the Evaluation Center judges that the said Japanese Phase III study could be conducted as a Phase IV study, or the target subjects could be restricted (to influenza type, target patients), or alternatively it would be possible to give approval subject to the imposition of approval conditions such as asking for the data missing at the present time to be provided as supplementary data.

Target patients who need this drug may easily be imagined to be the elderly, children, patients with asthma and chronic obstructive pulmonary disease (COPD) and pregnant women but data from currently ongoing clinical studies in the elderly and children (therapeutic and prophylactic administration) have yet to be submitted and moreover, as pregnancy is set as an exclusion criterion in the Japanese clinical studies, no data exist. Accordingly, we believe that the usefulness of zanamivir in the patient groups anticipated to need this drug has not been satisfactorily proven. In particular, the Evaluation Center considers that with a drug with a strong possibility that its clinical efficacy will be affected by how skilfully the patient can inhale it, very much more rigorous guidance will be needed in these patient groups than in adults about the fitting and changing of the rotadisc in the inhaler, how to break the blister and the method of inhalation.

One feature of zanamivir is held to be its anti-viral activity against influenza B which has been verified *in vitro*. However, in both the Japanese and foreign clinical studies, cases of influenza B accounted for 24% in the southern hemisphere, 1% in North America, 4% in Europe and 2% in Japan and no clinical studies looking at influenza B infection have been conducted. The Evaluation Center considers that the prophylactic efficacy of zanamivir upon inoculating healthy subjects with influenza B was not proved.

They also consider that this drug cannot be classed as a poisonous drug or powerful drug.

4. Results of documentary compliance survey by Drugs Organization and Evaluation Center decision

1) Decision of Evaluation Center on documentary compliance survey

To be given at a later date

2) Decision of Evaluation Center regarding GCP survey

To be given at a later date

Differences between placebo and zanamivir groups by primary endpoint (Attachment)

	Southern hemisphere (NAIB 3001) Phase III	Europe (NAIB 3002) Phase III	North America (NAIA 3002) Phase III	Japan Late Phase II 1
Number of cases	N=455 virus (+) 321, high- risk 76	N=356 virus (+) 277, high- risk 32	N=777 virus (+) 569, high- risk 10	N=244 virus (+) 225
Route of administration	Inhalation (diskhaler)	Inhalation (diskhaler)	Inhalation (diskhaler)	Inhalation (diskhaler)
Dose and period of administration	10 mg, b.i.d. x 5 days	10 mg, b.i.d. x 5 days	10 mg, b.i.d. x 5 days	10 mg, b.i.d. x 5 days (119) 20 mg, b.i.d. x 5 days (125)
Treatment initiation from symptom onset	Within 36 hours	Day 1 or day 2	Day 1 or day 2	Within 36 hours
Primary endpoint	Fever, headache, myalgia, cough, sore throat	Fever, headache, myalgia, cough, sore throat	Fever, headache, myalgia, cough, sore throat	Fever , headache, myalgia
Median to symptom alleviation (virus (+))	Placebo 6 days , Zanamivir 4.5 days <u>p=.004</u>	Placebo 7.5 days , Zanamivir 5 days <u>p <.001</u>	Placebo 6 days , Zanamivir 5 days p=.078	Placebo 4 days , Zanamivir 4 days p=.4696
Median to symptom alleviation (intent to treat)	Placebo 6.5 days , Zanamivir 5 days <u>p=.011</u>	Placebo 7.5 days , Zanamivir 5 days <u>p <.001</u>	Placebo 6 days , Zanamivir 5.5 days p=.228	Placebo 4 days , Zanamivir 4 days p=.2528
Median to symptom alleviation (high risk)	Placebo 8 days , Zanamivir 5.5 days <u>p=.048</u>	Placebo 11.5 days , Zanamivir 9 days p =.178	Placebo 6.5 days , Zanamivir 7.5 days p=.710	—
Median to symptom alleviation (high risk + virus (+))	Placebo 8.3 days , Zanamivir 5 days p=.161	Placebo 11.5 days , Zanamivir 9.25 days p=.21	Placebo 6 days , Zanamivir 6.25 days p=.886	—
Median to symptom alleviation (virus (–))	Placebo 7 days , Zanamivir 6.75 days p=.486	Placebo 7 days , Zanamivir 5.25 days p=.551	Placebo 5 days , Zanamivir 6 days p=.712	—

(Underlined: significant difference found (p<.05))

4 October 1999

EVALUATION REPORT (2)

Pharmaceuticals and Medical Devices Evaluation Center

1. Product Summary

[Proprietary name]	Relenza
[Generic name]	Zanamivir hydrate
[Date of application]	2 August 1999 (application for import approval)
[Applicant]	Glaxo Wellcome
[Dosage form, content]	Inhaled powder One blister = one product unit Containing zanamivir hydrate as 5 mg zanamivir per blister.
[Uses]	Infection with Influenza A or B
[Dosage and Administration]	Children aged 12 and over and adults usually inhale 10 mg per dose as zanamivir (2 x 5 mg blisters) twice daily for 5 days using a special inhaler
[Special note]	Priority Evaluation

2. Outline of submitted data and summary of evaluation by Evaluation Center

ii Data on physicochemical properties and data on specifications and test methods etc.

The Evaluation Center considered that the hygroscopicity of the drug substance (zanamivir hydrate) could pose a problem for the properties of the product. When they asked why zanamivir hydrate ** had been selected, the reply was given that it had been selected from the point of view of **. However, because it had not been made clear in the approval application that the drug substance for this product is **, they asked for ** to be described in the section on production method and upon being told that this would be done, accepted this. Furthermore, as some of the items in the identification tests for the drug substance failed to distinguish the drug substance (zanamivir hydrate) from **, they asked for the setting of ** to be investigated.

When the Evaluation Center asked about the route whereby the 5 mg/blister product had finally been chosen because three types of dosage form had been used in the clinical studies, the course of the product design was explained and as fresh data concerning product design were submitted, the response was accepted.

Upon querying whether there was a need to set specifications for ** in Japan, a response to the effect that ** was provided.

The Evaluation Center considered that because this drug is a preparation to be inhaled by the inspiration of the patient him/herself, the reliability of inhalation would be increased by providing appropriate guidance and information on use. They judged there to be a need to provide patients with rather fuller information.

iii Data regarding stability

When the Evaluation Center asked whether it was valid to set ** as ** material had been found in the long term study on the drug substance, the reply was given that this had been caused by ** and that the setting of ** was valid. With the observed values for ** in the preparation as well, because there had been considerable variation in the measurements and the investigations of ** in the analytic procedure validation had been inadequate, they requested a reassessment of whether the specification values by this test method had been set properly.

iv Data regarding acute toxicity (single dose), subacute and chronic toxicity (multiple dose), teratology (reproductive and developmental toxicity) and other forms of toxicity

The overall toxicity studies had been conducted as spray inhalation studies using liquid and powder agents in the inhalation studies. When the Evaluation Center enquired why different preparations had been used, they were told that this was because the development dosage form had been changed mid-term during the studies but that care had been taken to keep the drug substance at a constant level in each test. This was accepted.

When they asked whether any abnormalities in respiratory condition due to administration of the drug had been seen, the reply was given that changes in respiratory condition had been observed sporadically at an extremely low frequency but as the same had been observed with the vehicle control, they were thought not to be due to the administration of zanamivir. This was accepted.

When they asked whether there was any relationship between the degree and frequency of the 'reddening of the ears and gums' and dose seen in the various studies, they were told that there had been no correlation with the dose and accepted this response.

In the single dose and multiple dose toxicity studies, one control group animal had been used in substitution for a test animal which had died in the rat intravenous study. When the Evaluation

Center questioned the validity of this, the reply stated that this had been done on the basis of FDA GLP and UK GLP standards and that they believed that the GLP compliance of the study was assured. They accepted this response.

When they asked whether the vomiting seen in the dog 8-day inhalation study had been an effect of zanamivir, they were told that as this had occurred transiently in the medium dose group and dogs are by nature prone to vomiting in toxicity studies, it was not considered to be an effect of the drug. They accepted this response. Moreover, upon asking whether it had been confirmed that no zanamivir had been detected in the plasma of non-dosed and vehicle-dosed animals, they were told that this had been confirmed and as well as accepting this, additionally had ** noted.

The Evaluation Center asked whether the gasping and congestion of the lungs seen in the rat 1-month inhalation study had been effects of zanamivir and for the reason why, when a high dose female had been killed *in extremis* on the first day following completion of dosing due to gasping and pallor of the extremities, this case had not been used as evidence when estimating the non-toxic dose. They were told that this had been an adventitious change caused by the method of administration and was not considered to be an effect of the drug and so the animal had not been used as evidence for setting the non-toxic dose. This response was accepted. Furthermore, when they asked for a detailed explanation of the fact that the rise in MCV had been held to be of little toxicological significance, they were told that it had been judged to be of little toxicological significance because it had been within the range of variation in the control groups (air and lactose). This response was accepted.

Soft feces had been observed in the dog 1-month intravenous study and upon asking whether the degree and frequency thereof were correlated to the dose level, they were told that there had been no dose correlation and accepted this response. When they asked for an explanation of the mechanism for the alveolar macrophage infiltration seen in the rat 6-month inhalation study, they were told that it had been due to the particles and was not something caused by the drug. This response was accepted.

When the Evaluation Center asked for the results for each lobe for the bronchial lumen fibrosis and inflammation seen in the histopathological investigations in the dog 6-month inhalation study to be

given whilst setting out any dose correlation, they were told that the mechanism involved, inflammatory cell infiltration, decreased infiltrating cells, fibroblast cell development and fibrosis but that there had been no correlation with dose and it had been judged to be an adventitious finding. This response was accepted.

As regards the reproductive and developmental toxicity studies, the Evaluation Center enquired why, in the tests to check the effects on behavioral function seen in F1 males in the fertility and general reproduction studies, dosing had continued throughout the lactation period in the former whereas the dosing period had been taken as the gestation period in the latter. A reply was received to the effect that the aims of the studies had been different, with the latter seeking to observe behavioral abnormalities deriving from the effect of the development and differentiation of physical function during the foetal period. This response was accepted.

Upon asking for details of the teratology seen in rats and rabbits in the fetal organogenesis study, they were told that there had been no correlation with dose, and that as there was no bias towards specific teratology and it had occurred mainly in the same litter, it was concluded to have occurred spontaneously. This response was accepted.

Upon asking the reason why the mean plasma concentrations in the perinatal and lactation study were lower than in the fertility and general reproduction performance studies or the organogenesis study, they were told that the variations had been within the range which can normally arise due to individual differences or measurement error etc. and they accepted this response.

v Data regarding pharmacology

The Evaluation Center accepted the responses to the following points and had these noted **.

1) The reasons for using mainly ferrets as the experimental animals in the *in vivo* studies
2) The validity conducting most of the study by nasal instillation despite the fact that the actual method of clinical use is oral inhalation
3) The inhibitory action of zanamivir taking complex sugar chains, glycolipids or disaccharides as substrates
4) The reasons for the high affinity of zanamivir to influenza virus neuraminidase

5) The discussion about any correlation between the action on water and electrolyte metabolism noted in relation to the general pharmacology study results for zanamivir, and decreases in serum sodium noted in the dog 1 month study in the toxicity studies
6) The pharmacological activity and general pharmacological activity of impurities at the time of synthesis
7) The existence of data concerning the effects of zanamivir on ligand-receptor interactions

Although responding that the reason for selecting MDCK host cells had been that these were cultured cells widely used to investigated antiviral action, the applicant also replied that these cells are unsuitable for investigating the development of resistance in the clinical setting and that they are currently establishing an experimental system using new cultured cells.

The Evaluation Center pointed out the disparity in IC_{50} for inhibitory activity against plaque formation and for *in vivo* antiviral activity and the IC_{50} for neuraminidase inhibition and asked for a discussion of this. The response submitted stated that whilst there was a disparity between the IC_{50} for inhibitory activity against plaque formation and for *in vivo* antiviral activity and the IC_{50} for neuraminidase inhibition, a similar trend had been noted in the potency of the inhibitory action against the virus strain used and that it was valid to evaluate the efficacy of zanamivir with its neuraminidase inhibitory activity. The Evaluation Center investigated whether the reason why the efficacy of zanamivir had failed to be validated in the Japanese and US clinical studies despite its potent neuraminidase inhibitory activity could be explained from the *in vitro* and *in vivo* studies. They believe that the data submitted make clear that the concentration of zanamivir at which it will suppress the release of virus from infected cells needs to be more than the concentration at which neuraminidase is inhibited. The applicant submitted replies stating that as zanamivir acts extracellularly, the effective concentrations *in vitro* and *in vivo* will differ less than compared to drugs which manifest their activity upon being taken up into cells, and the concentration at which it suppresses neuraminidase in clinical practice will correspond to the concentration at which the drug manifests antiviral action, and that they recognize that there will be a difference in the concentration suppressing neuraminidase and the concentration inhibiting plaque formation. They considered that the cause of this was imprecision in the plaque formation inhibition tests. Then, if zanamivir does work extracellularly, an answer was sought as to how the drug is thought to reach the active site following inhalation in clinical practice, and what the anticipated extracellular concentration is.

However no data exist demonstrating whether zanamivir can diffuse satisfactorily from the mucosa of the lung into pulmonary tissue where the virus is multiplying. The applicant has estimated the amount reaching the lung from the residue of drug in the inhaler and compared this with the neuraminidase inhibitory concentration, but we believe that the responses lack scientific force. The Evaluation Center therefore believes that it is difficult to support the efficacy of zanamivir in clinical use from the non-clinical pharmacology study and that efficacy in the clinical setting needs to be validated separately.

We believe that investigation by the Subcommittee will be needed as to whether these judgements by the Evaluation Center are valid.

vi Data regarding absorption, distribution, metabolism and excretion

The Evaluation Center checked whether there are any 1) ADME data for Japanese elderly and child subjects and 2) data on the bioequivalence of nasal instillation and inhalation and accepted the reply that data for Japanese elderly subjects and foreign child subjects exist and that no bioequivalence study on nasal instillation and inhalation has been conducted.

Upon comparing the Japanese and foreign pharmacokinetic parameters in man, $t_{1/2}$ and AUC in Japan following a single 10 mg inhalation dose were about one half the levels seen overseas and even when the single dose was increased to 20 mg, $AUC_{0-‡}$ rose only to 508.5 ± 83.1ng.hr/mL. In view of this, the Evaluation Center believed that the possibility could not be ruled out that inhalation by the diskhaler had been inadequate and that most of the drug had been absorbed from the gut and not in the lungs. The applicant provided a reply stating that absorption of zanamivir from the gut is 2%, and that as there is no difference in renal excretion in Japan and overseas, the amount of drug excreted in the urine will reflect the amount of drug passing into the blood through the lungs and the urinary excretion ratios in Japan and overseas do not differ. Moreover, the differences in blood concentrations seen in Japan and overseas were commonly due to the variation of individual differences and not related to ethnic differences nor to skill level, and so a sufficient quantity of zanamivir would reach the lungs.

However, the course of serum concentrations in the 5 gm and 10 mg zanamivir single dose groups in Japan was respectively about one half and about one third that seen overseas and it was clear that even allowing for variation, the serum concentrations in the overseas 5 mg group corresponded to

the Japanese 10 mg group. Thus even if 10 mg were inhaled in a dose, in the Japanese clinical study, only an amount corresponding to 5 mg overseas would have reached the lungs and there is no option but to regard this as a reason why the efficacy of zanamivir could not be verified in the Japanese clinical studies (the lower single dose limit in the overseas clinical studies was 10 mg).

We believe that investigation by the Subcommittee will be needed as to whether these judgements by the Evaluation Center are valid.

vii Data regarding clinical study findings

[Clinical ranking of zanamivir]

When the Evaluation Center enquired about the grounds for claiming that a shortening of influenza symptoms by 1-2 days by zanamivir was clinically significant, the applicant asserted the following in respect of the drug's clinical significance; 1) that unlike the administration of conventional anti-inflammatory analgesics etc. for symptomatic alleviation in influenza infection, zanamivir inhibits the proliferation of the virus itself and can be expected to eliminate the symptoms of influenza beginning with fever early on, and that it may also be expected that spread of infection would be controlled due to the reduction in the quantity of virus particles discharged and shortening of the discharge time from infected persons; 2) that by using zanamivir in high risk populations such as the elderly, this not only treats the high risk population itself, but also, by removing infection factors from the environment around high risk populations at an early stage, reduced risk of infection may be anticipated; 3) unlike amantadine which is currently used in Japan for influenza virus infection, zanamivir is also effective against Influenza B and it is held that it would be difficult for viruses resistant to zanamivir to appear; and 4) compared to vaccination against the influenza virus, the effect of zanamivir is not governed by the prevailing strain. The Evaluation Center judged that the clinical significance of zanamivir is unclear because 1) the effect in controlling the spread of influenza by administering zanamivir to patients with influenza infection has not been proved in clinical trials at the present time, 2) the efficacy of zanamivir in high risk groups does not appear to be clear in the foreign and Japanese clinical studies and 3) in view of the fact that no therapeutic or prophylactic efficacy against Influenza B was found in the foreign clinical pharmacology study and from the results of the foreign Phase III and Japanese Phase II studies, it seems difficult to judge that zanamivir is clearly effective against Influenza B.

[Japanese clinical studies]

The clear efficacy of zanamivir in respect of the primary endpoint was not proven in the early and late Phase II studies conducted in Japan but the applicant asserts that the efficacy of the drug has been satisfactorily demonstrated in the foreign Phase III studies submitted as application data. The Evaluation Center judges that the efficacy of zanamivir in Japan cannot be proved by extrapolating the foreign study results because 1) the pharmacokinetics of zanamivir in the blood upon inhalation in man are different in Japan and overseas and 2) in the Japanese late Phase II dose finding study, the efficacy of zanamivir was not proved in comparison to placebo and the effective dose could not be determined. They therefore believe that the Phase II dose finding study in Japan needs to be conducted again.

The Evaluation Center asked the reason why usefulness had been evaluated in the Japanese Phase II study with three influenza symptoms (fever , headache, myalgia) as the primary endpoint, whereas overseas, the primary endpoint had been the evaluation of five symptoms (fever, headache, myalgia, cough, sore throat). The applicant replied that at the time when the primary endpoint for Japan had been set, the primary endpoint for the Phase III studies had not been established and as that as efficacy had been found in the Japanese Phase II study with its 3-symptom primary endpoint in the zanamivir group (inhalation + intranasal and inhalation only), the 3-symptom primary endpoint had been set for the late Phase II study. The Evaluation Center accepted this.

[Method of zanamivir administration]

It would seem to take some time for patients to acquire the proper method of inhaling zanamivir and the Evaluation Center queried whether any delay in becoming accustomed to the inhalation technique could possibly disrupt the timing of the therapy. The applicant replied that in the Japanese late Phase II study, as a result of the investigator etc. giving guidance to the patient on inhalation using a practise placebo, mean drug compliance in the 2 inhalations/dose group was 95.5% and it was possible for patients rapidly to acquire the inhalation technique. Because variations had been noted between individuals in the pharmacokinetic investigations on zanamivir, the Evaluation Center thought that there were individual differences in the airway distribution of the drug due to inhalation. There therefore seemed to be cases who failed to inhale the drug properly into the airway. As regards guidance on the inhalation method, the applicant replied that they were in the process of preparing an explanatory leaflet about inhalation for patients and an inhalation guidance leaflet for doctors and pharmacists. The

Evaluation Center judged that as there is no means of confirming that the drug has been properly inhaled into the airway, it is unsatisfactory only to have guidance on the inhalation method. We believe that investigation by the Subcommittee will be needed as to whether these judgements by the Evaluation Center are valid.

The Evaluation Center further asked the reason why, despite the fact that it had been anticipated that the therapeutic effect would be potentiated by the concomitant use of intranasal administration and inhalation when looking at the mechanism of action of zanamivir, the clinical efficacy of concomitant intranasal administration and inhalation had not been proved to be superior. The applicant replied that the contribution of intranasal virus to the manifestation of influenza symptoms is small and that virus proliferating in the airway mucosa in the lungs is the principal cause of them. The Evaluation Center considered that in view also of the fact that no significant therapeutic effect had been found in the concomitant intranasal administration and inhalation group in the Japanese early Phase II study, the reason why concomitant intranasal administration and inhalation had not been proved to be superior in Japan and overseas was that the clinical studies had not been conducted in a sufficient number of cases in order to detect differences in therapeutic effect. There therefore also appeared to be a possibility that the optimum method of administration for zanamivir had not been determined.

[Safety]

There was a possibility that the placebo group had not appropriate in terms of looking at safety and because it was feared that any differences in the incidence of adverse events compared to the zanamivir group would have been indistinct, the Evaluation Center asked about this point. The applicant replied that no pharmacological activity or irritation had been reported for the lactose used as the placebo for zanamivir and that as no toxicologically significant signs had been noted in the lungs during the 6-month inhalation study with lactose in rats and dogs, the lactose preparation placebo could be regarded as a true placebo. The Evaluation Center accepted this response.

[Validity of Dosage and Administration and Precautions and Warnings]

The Evaluation Center asked about the validity of having cases aged 12 and over as targets for the drug despite the fact that cases under 16 years had not been treated in the Japanese studies. They were told that the efficacy and safety of zanamivir could be satisfactorily assured from the results of the foreign Phase III study. The Evaluation Center judges that the results of the foreign clinical studies cannot be extrapolated and that because trials on zanamivir have been conducted in cases aged 16 and over, they believe that safety is not assured in those under 16.

The applicant also responded that they would include in the Precautions and Warnings (draft) and package insert (draft) that 1) the kinetics of zanamivir in patients with hepatic and renal impairment have not been investigated, 2) safety in cases of severe renal compromise is not proven, 3) usefulness is not proven if treatment is initiated more than 48 hours after the onset of influenza symptoms, 4) safety in cases of bronchial asthma or chronic obstructive pulmonary disease is not proven, 5) at the present time, no efficacy has been found with prophylactic use and 6) restrictions on the use of zanamivir in possibly pregnant or pregnant women and lactating women. The Evaluation Center accepted these.

3. Results of documentary compliance survey by Drugs Organization and Evaluation Center decision

1) Decision of Evaluation Center on documentary compliance survey

To be given at a later date

2) Decision of Evaluation Center regarding GCP survey

To be given at a later date

4. Overall evaluation of Evaluation Center

The Evaluation Center considers from the data submitted that the efficacy of zanamivir has been verified in Europe and the southern hemisphere. However, they believe that the Japanese trials up to late Phase II have failed to verify the efficacy of the drug. They consider that in order to bridge between the Japanese data and foreign data, there is a need to address the problems in the Japanese clinical trials at the present point and in future studies in Japan, to conduct appropriate trials and so establish the optimum dose for Japan as well as verifying efficacy.

The Japanese data currently submitted are thus inadequate to permit bridging to the foreign data and at the present point in time, the Evaluation Center considers that it is difficult to judge the efficacy of zanamivir in Japan.

11 November 1999

SUMMARY OF SUBCOMMITTEE DELIBERATIONS

Fourth Subcommittee on New Drugs

1. Deliberation process

Meeting held: 30 August 1999 (first meeting)

Meeting held: 18 October 1999 (second meeting)

Subcommittee conclusion: We consider that in order to bridge between the Japanese data and foreign data on zanamivir, there is a need at least for the efficacy of the drug to be verified in Japanese clinical trials and for communality of the Japanese dose finding study and foreign clinical study data to be demonstrated. We believe that the results of the late Phase II study conducted in Japan fail to prove the efficacy of zanamivir and that at the present point in time, it is difficult to judge the efficacy of zanamivir in Japan.

However, to the extent that we can evaluate studies conducted in Europe and the southern hemisphere, it would seem that efficacy has been proved in these regions and we have decided to pass the matter to a Special Subcommittee in view of the social need for this drug. If the Special Subcommittee concludes that 'the approval of zanamivir is warranted', we believe the approval conditions outlined below must be attached.

2. Subcommittee Report

A Phase III clinical trial on zanamivir has not been conducted in Japan and an application has been made on the basis of the findings of three Phase III studies conducted overseas (southern hemisphere, US and Europe) and bridging to the findings of a Japanese late Phase II study.

As a results of deliberation in the Fourth Subcommittee on New Drugs regarding the Japanese and foreign clinical study findings for zanamivir, the Subcommittee judged that the following two items needed to be satisfied at least as prerequisites.

1. The existence of results demonstrating the efficacy of zanamivir in the European and southern hemisphere parts amongst the foreign findings

2. In order to extrapolate such foreign findings to the Japanese findings and discuss the efficacy and safety of zanamivir

1) Results must be obtained demonstrating that the results for pharmacokinetics in the Japanese studies are similar to the foreign findings, and

2) Findings by which efficacy can be verified prospectively must be present in the Japanese clinical studies

Based on the above judgements, responses were sought from the applicant regarding the points summarized below.

(1) The efficacy in the Japanese Phase II study has failed to be validated in a placebo-controlled study. Accordingly, to bridge to the foreign data, we consider that the Phase II dose finding study in Japan needs to be repeated. Present a plan for such a Japanese clinical trial.

(2) Clear differences have been demonstrated in the serum concentration-time course of the drug in Japanese and foreign subjects, with Cmax in Japanese subjects being one half and AUC one third to one quarter the levels seen in foreign subjects. These differences in inhalation parameters would seem to depend on differences in the amount reaching the lungs due to the inhalation technique. Clarify the reasons why foreigners inhaled more (why more reached the lungs) and the grounds for concluding that the foreign findings could be extrapolated despite there seeming to be differences in the arriving amount as a basic condition for inhaled agents.

(3) There are judged to be no findings proving the efficacy of zanamivir taking the primary endpoint as the indicator throughout all three Japanese clinical studies. On the premise that the pharmacokinetics of zanamivir are clearly different in Japan and overseas, establish if the reason why efficacy could not be proved in the Japanese studies was that the amount of drug reaching the lungs was a fraction of the amount overseas.

(4) In the Japanese early Phase II study, whereas efficacy in the IH+IN (inhalation) group would have been expected to be equivalent or superior to the IH (nasal spray) group, the actual result conversely was that the IH+IN was inferior. No significant difference from placebo was achieved either. Give the applicant's interpretation of how the efficacy of zanamivir should be viewed in the light of these findings.

(5) In the Japanese early Phase II study, no significant difference from placebo was achieved in the per-protocol and influenza-positive sets, which would seem to be the most reliable in terms of efficacy evaluation, in both the IH and IH+IN groups. Give the applicant's interpretation of how the efficacy of zanamivir should be viewed in the light of these findings.

(6) In the Japanese late Phase II study, for the FAS which formed the principal object of analysis, no significant difference from placebo was achieved whether for three or five major symptoms. Give the applicant's interpretation of how the efficacy of zanamivir should be viewed in the light of these findings.

(7) In the Japanese late Phase II study, in the EFF group for which reliability would seem to be highly reliable for the evaluation of efficacy (cases evaluable as influenza virologically in the protocol, efficacy population), no significant difference from placebo was achieved whether for three or five major symptoms. Give the applicant's interpretation of how the efficacy of zanamivir should be viewed in the light of these findings.

(8) As the foreign Phase III study indicated superior therapeutic efficacy in the placebo group in non-white subjects, it would seem that endogenous racial factors such as genetic polymorphism and differences in lifestyle etc. cannot be ignored. Give the applicant's thoughts on this point.

(9) It would appear that the clinical studies overall fail to prove efficacy against Influenza B. Clarify the grounds for claiming that zanamivir is effective in Influenza B.

(10) In view of the fact that the foreign data are insufficient for the 'high risk group including the elderly and children' who have a need for this drug, we believe that data verified in Japan are necessary and vital. Give the applicant's view on this point.

(11) It would seem that the absorption and excretion mechanisms are different with the inhaled agent than with the intravenously injected drug. Clarify the pharmacokinetics of zanamivir in the airway.

The applicant provided the following responses to the above.

(1) No statistically superior results were found with zanamivir compared to placebo for the rapidity of alleviation of the three major symptoms in the FAS forming the primary endpoint. However, in that a trend was seen for the five major symptoms in the EFF amongst the secondary endpoints to be alleviated more quickly. As there are no grounds for claiming that these findings were inferior to the foreign results, the efficacy of zanamivir was demonstrated and there is no need to repeat the study.

(2) They believe that differences in pharmacokinetics seen between the Japanese and foreign data were due not to ethnic differences but to variation between subjects.

(3) They do not consider that the efficacy of zanamivir could not be proved in the Japanese study because the amount of the drug reaching the lungs was less than overseas. They consider that the efficacy of zanamivir is supported by the present clinical studies as in response (1) above.

(4) For the five major symptoms including cough, the results indicated that the alleviation rate was inferior as detection sensitivity had fallen over the 5-day observation period.

(5) No significant difference was achieved in the per-protocol, influenza-positive group. The cause of this would seem to be the effect of the smaller number of cases evaluated.

(6) No significant difference was achieved between zanamivir and placebo for either the major 3 symptoms or 5-symptoms in the FAS. However, an effect was seen in the size of change in body temperature.

(7) In the EFF, no statistically significant difference was obtained compared to placebo for the rate of alleviation of the 3 major symptoms. However, a trend towards difference was seen for the 5 symptoms.

(8) In the North American study, zanamivir had been inferior to the placebo in the non-white, influenza-positive population. However, the results in this study were for only 74 cases when both groups were combined and no statistical investigation could be undertaken so that they believe this to have been a chance result.

(9) There were only 47 cases of Influenza B in Japan. In the early Phase II study, no significant difference from placebo had been achieved for either the 3 or 5 major symptoms. Overseas too, there were few cases of Influenza B but statistical analysis of the foreign Phase III study indicated that the median value for the day of influenza symptom alleviation was significantly superior.

(10) A placebo-controlled comparative study would seem desirable to evaluate the efficacy of zanamivir. However, as it may be considered that there would be few cases in Japan from whom subject co-operation would be obtained, it is estimated that it would take 3 or more years to complete the study.

(11) The kinetics of zanamivir in the trachea or bronchi are unclear.

Having reviewed the above responses, we judged that the responses were unsatisfactory in respect of two points essential to the evaluation of zanamivir, namely

1. Bridging with a Phase II dose finding study is essential for zanamivir whose pharmacokinetics appear to be different in Japan and overseas from the study findings submitted

2. As a premise for bridging, the existence of findings prospectively proving the efficacy of zanamivir in a Japanese clinical study will be essential

We have accordingly concluded that the findings up to the late Phase II study conducted in Japan do not verify the efficacy of zanamivir.

However, in view of the fact that

1. Amongst the studies conducted overseas, some results from Europe and the southern hemisphere have provided results indicating the efficacy of zanamivir, and
2. There is a social need for this drug

we have decided as the Fourth Subcommittee on New Drugs to pass on the above conclusions and seek a review by the Special Subcommittee concerning whether or not to give approval.

If the Special Subcommittee were to conclude that 'Approval of zanamivir is warranted', we consider that approval conditions such as shown below should be attached due to the need to verify the efficacy and safety of zanamivir further etc.

[Approval conditions]

1) Appropriate postmarketing surveillance to verify the efficacy and safety of zanamivir must be undertaken and interim analysis conducted at 3 years, the results of which must be presented to the regulatory authorities without delay

The progress of the survey must be reported at regular intervals (every six months)

2) An appropriate postmarketing clinical study must be undertaken without delay and the optimum dose of zanamivir for Japan established.
3) The pharmacokinetics of zanamivir in Japan must be established in Japan without delay.
4) Medical workers must provide patients using zanamivir with satisfactory information about the handling of the inhaler, including guidance such as through demonstrations using a placebo.
5) As the efficacy of zanamivir in high risk groups in Japan is not yet proven, the definitions and criteria for high risk groups in clinical trials to date must be clarified and a Japanese clinical trial focusing on high risk groups conducted.
6) The findings for clinical trials in high risk patients conducted overseas must be reported to the regulatory authorities as they become available.
7) Results of the ongoing foreign survey on the development of resistance to zanamivir must be reported to the regulatory authorities as they become available.

8) If there is any change overseas in the uses, dosage and method of administration and precautions and warnings, having notified the regulatory authorities without delay, appropriate information must be provided in the field.

The Subcommittee has further decided to attach the following guidance.

[Guidance]

1) This application has been made on the premise of bridging to the foreign data but in order to do this, the efficacy of zanamivir needs to be proved prospectively in a Japanese clinical study. As the efficacy of zanamivir in Japan claimed by the applicant is not recognized for reasons (1) – (2) below, an appropriate postmarketing clinical trial must be conducted and the efficacy of the drug proved.

   (1) In the early Phase II study, whilst the ITT population which formed the main evaluation population was significantly superior to the placebo group, in late Phase II study 1, a tendency was seen for the EFF population which formed the secondary evaluation population (those judged to be influenza-positive amongst the protocol compatible cases) to be superior to the placebo group in the rapidity with which the 5 symptoms were alleviated and no harmonization of the subjects for efficacy analysis is apparent.

   (2) For ITT for which significant difference was seen in the early Phase II study, in late Phase II study 1 which investigated a larger number of cases and may be considered to be more reliable, there was no difference in response rate from placebo for the FAS which corresponded to ITT.

   (3) The rapidity with which 3 symptoms were alleviated, which formed the primary endpoint in late Phase II study 1, showed even no trend difference from the placebo group even by EFF. In the early Phase II study, analysis of the influenza-positive, per-protocol set corresponding to EFF showed even no difference of trend from placebo.

   (4) Retrospective analysis the Japanese clinical studies matching the evaluation criteria in the foreign Phase III study must not indicate any evidence that they are inferior to the overseas findings. It must be stressed that retrospective analysis may be interpreted as reference data only.

2) From the data provided to date, the pharmacokinetics of zanamivir are not equivalent in Japan and overseas and lower bioavailability is apparent with multiple doses.

The applicant claims that these were due to variation between subjects but reliable study findings with little variation need to exist for any discussion of pharmacokinetics. Moreover, even if there were variation between subjects, we believe that there is little scientific evidence for the claim that a sufficient quantity of the drug was reaching sites in the trachea, bronchi and lungs because the pharmacokinetics in the trachea and bronchi are unclear.

In consideration of the above, a Phase I clinical study must be conducted again in Japan on the basis of reappraisal of the study method.

3) In the non-white set of the influenza-positive population in the North American study, the zanamivir group with 5-symptom alleviation in 5.75 days performed less well than the placebo group with 5-symptom alleviation in 5.25 days. No statistical investigation was undertaken because the number of cases involved had been only 28 and 36 respectively and the reason for the result was considered to be chance. As against this, in the Japanese studies the early Phase II study had been conducted with 31 complete cases in the inhalation group and 31 in the placebo group, an IP analysis population in late Phase II study 1 (the FAS population judged to be influenza-positive) comprising an application dose group of 71 cases and placebo group of 72. Late Phase II study 2 was conducted with 19 cases in the application dose group and 16 in the placebo group. No contradictory analysis must be performed taking the North American findings to be chance results due to the small number of cases but the Japanese study results based on much the same number of cases to be valid.

The urinary excretion ratio of zanamivir appeared to be about 1.5 times higher in foreigners than in Japanese and taking the view that most of the drug excreted in the urine has been distributed and absorbed in the lungs, the amount distributed to the lungs in Japanese subjects may be inferred to be about 1/1.5 times that in foreigners. Assuming there to be no ethnic differences in excretion, it may be thought that differences in the anatomical structure of the nasal cavity etc. were affecting distribution in the airway and hence drug potency.

In that the findings in the North American studies provide valuable data for extrapolating the usefulness of zanamivir to Japanese subjects from the foreign results, the applicant's views must be given again regarding the effects of differences in endogenous ethnic factors or lifestyle showing the detailed ethnic proportions, such as the proportion of Asians.

4) It must be considered that the efficacy of zanamivir in Influenza B has failed to be proved from the data provided to date.

5) If there are any immunological data about influenza due to the use of zanamivir, such as showing that the use of zanamivir has reduced mortality rates from influenza, this must be presented.
6) Set out the detailed definition and validity of using the 'risk ratio' employed in the statistical analysis of the clinical studies. Moreover, in the investigation of interactions in the three foreign Phase III studies, explain the reasons why an 'odds ratio' based on a 'proportional odds model' and not a 'risk ratio (hazard ratio)' based on a proportional hazard model was used.
7) Supposing that the approval conditions were attached by the Special Subcommittee on Drugs, having verified the efficacy and safety of zanamivir from the results of the 3 year interim analysis, we believe there will be a need to conduct a Japanese clinical study to broaden the applications to children. The applicant's view on this point should be stated.
8) The specifications and test methods for zanamivir must be re-adjusted to the form of quality standards used in Japan.
9) If zanamivir were to be approved, excessive promotional activity must not be undertaken as there is little scientific basis for claiming that it is a "special drug for influenza" or a "special drug for Influenza B".
10) If zanamivir were to be approved, postmarketing surveillance must be undertaken to check that it is being inhaled properly.

The Fourth Subcommittee on New Drugs also reviewed whether or not to limit the targets for zanamivir to the high risk groups in which it may be expected to be most needed. However, as the efficacy and safety of zanamivir in high risk groups have not been proved from the data submitted on this occasion, they concluded that there was no reason to limit the targets for the drug to the high risk groups.

The following problems remain outstanding from the responses submitted.

1) The explanation from the applicant cannot be said to be satisfactory about why two approaches, i.e. 'hazard ratio based on a proportional hazard model' and 'odds ratio' based on a proportional odds model' were adopted in the statistical analysis of the clinical studies. The assertion in the present application data that there is no difference between the studies on the basis of the fact that the interaction item in the models was not significant, is invalid.
2) The kinetics of zanamivir in the trachea or bronchi are unclear and no response has been given to the fact that as the urinary excretion of the drug is 1.5 times higher in foreigners than in

Japanese, distribution to the lungs in Japanese subjects may be inferred to be 1/1.5 of the foreign level.

3) From the foreign Phase III study, it would seem that endogenous racial factors such as genetic polymorphism and differences in lifestyle etc. cannot be ignored but a response stating that 'there is no difference' was given without conducting scientific analysis.

9 November 1999

EVALUATION REPORT (3)

Pharmaceuticals and Medical Devices Evaluation Center

1. Summary of review beyond initial Subcommittee meeting

1) Outline of submitted data and summary of evaluation by Evaluation Center

ii Data on physicochemical properties and data on specifications and test methods etc.

When the Evaluation Center asked for the setting of the identification tests by ** to be investigated because the identification tests for the drug substance do not distinguish the drug substance (zanamivir hydrate) from ** in any item, they were told that the setting of the identification tests is being discussed with Glaxo-Wellcome of the UK.

iii Data regarding stability

From the validation of matters such as precision and reproducibility of the liquid chromatography for ** in the drug substance and product, the Evaluation Center requested reassessment of whether the specification values by this test method had been set properly. A reply was received that the quantitation method and ** in the test would be changed to ** and the specification values for both the drug substance and product would be set more strictly. This was accepted.

iv Data regarding acute toxicity (single dose), subacute and chronic toxicity (multiple dose), teratology (reproductive and developmental toxicity) and other forms of toxicity

The Evaluation Center asked for an explanation of the mechanism of alveolar macrophage infiltration seen in the rat 6-month inhalation study and was told that this had been due to the particles and had not been caused by the drug. This response was accepted.

v Data regarding pharmacology

The Evaluation Center asked how, if zanamivir acts extracellularly, it was considered to reach the active site after being inhaled, and what are the anticipated extracellular concentrations in the lungs. However, no data exist demonstrating whether zanamivir can diffuse satisfactorily from the mucosa of the lung into pulmonary tissue where the virus is multiplying. The applicant has been estimating the amount reaching the lungs from the residue left in the inhalation device and comparing this with

the neuraminidase inhibitory concentration but we felt that these responses lacked scientific force. A decision that this view of the Evaluation Center was valid was received from the Subcommittee.

vi Data regarding absorption, distribution, metabolism and excretion

The course of serum concentrations in the 5 gm and 10 mg zanamivir single dose groups in Japan was respectively about one half and about one third that seen overseas and it was clear that even allowing for variation, the serum concentrations in the overseas 5 mg group corresponded to the Japanese 10 mg group. Thus even if 10 mg were inhaled in the dose, in the Japanese clinical study, only an amount corresponding to 5 mg overseas would have reached the lungs and there is no option but to regard this as a reason why the efficacy of zanamivir could not be verified in the Japanese clinical studies (the lower single dose limit in the overseas clinical studies was 10 mg). A decision that these judgements of the Evaluation Center were valid was given by the Subcommittee.

vii Data regarding clinical study findings

[Clinical ranking of zanamivir]

The Evaluation Center judged that the clinical significance of zanamivir is unclear because 1) the effect in controlling the spread of influenza by administering zanamivir to patients with influenza infection has not been proved in clinical trials at the present time, 2) the efficacy of zanamivir in high risk groups does not appear to be clear in the foreign and Japanese clinical studies and 3) in view of the fact that no therapeutic or prophylactic efficacy against Influenza B was found in the foreign clinical pharmacology study and from the results of the foreign Phase III and Japanese Phase II studies, it seems difficult to judge that zanamivir is clearly effective against Influenza B. The Subcommittee likewise judged that clinical effects such as clearly reducing mortality due to influenza virus infection in groups treated with zanamivir has not been demonstrated and that the clinical significance of zanamivir is unclear.

[Japanese clinical studies]

The clear efficacy of zanamivir in respect of the primary endpoint was not proven in the early and late Phase II studies conducted in Japan but the applicant asserted that the efficacy of the drug had been satisfactorily demonstrated in the foreign Phase III studies submitted as application data. The Evaluation Center judged that the efficacy of zanamivir in Japan cannot be proved by extrapolating the foreign study results because 1) the pharmacokinetics of zanamivir in the blood upon inhalation in man are different in Japan and overseas and 2) in the Japanese late Phase II dose finding study, the efficacy of zanamivir was not proved in comparison to placebo and the effective dose could not be

determined. They therefore believed that the Phase II dose finding study in Japan needed to be conducted again. The Subcommittee likewise judged that the efficacy of zanamivir in Japan had not been verified versus placebo. They instructed that "No contradictory analysis must be performed taking the North American findings to be chance results due to the small number of cases but the Japanese study results based on much the same number of cases to be valid" and judged that the Phase II dose finding study in Japan needs to be repeated.

[Method of zanamivir administration]

The Evaluation Center judged that as there is no means of confirming that the drug has been properly inhaled into the airway, the guidance on the inhalation method on its own in unsatisfactory. The Subcommittee judged that the pharmacokinetics of this drug as an inhaled agent have not been established because the mechanism of foreign material excretion due to ciliated epithelial movements plays an important role in the absorption and excretion of drugs inhaled through the airway.

The Evaluation Center believed that the reason why the clinical effect of combined intranasal administration and inhalation had not proved to be superior in Japan and overseas was that the clinical trials had been conducted in an insufficient number of cases to detect differences in clinical response. They therefore thought there was a possibility that the optimum dose of zanamivir had not been determined. The Subcommittee also judged that the efficacy of zanamivir had not been verified because no significant difference from placebo had been found in the zanamivir inhalation only and combined intranasal and inhalation groups.

[Validity of Dosage and Administration and Precautions and Warnings]

The Precautions and Warnings (draft) were investigated on the basis of the above judgements.

Additionally, having obtained a response that the applicant would include in the Precautions and Warnings (draft) and package insert (draft) that 1) the kinetics of zanamivir in patients with hepatic and renal impairment have not been investigated, 2) safety in cases of severe renal compromise is not proven, 3) usefulness is not proven if treatment is initiated more than 48 hours after the onset of influenza symptoms, 4) safety in cases of bronchial asthma or chronic obstructive pulmonary disease is not proven, 5) at the present time, no efficacy has been found with prophylactic use and 6) there should be restrictions on the use of zanamivir in possibly pregnant or pregnant women and lactating women. These were to be added to the Precautions and Warnings.

The foreign studies had looked at cases aged 12 and over, the Japanese studies at those aged 16 and over. The Evaluation Center therefore judged that the safety of zanamivir in children had not been confirmed and that the target age for zanamivir in Japan should be 16 and over, the same age as the subjects in the Japanese clinical trials. The Subcommittee determined that the use of zanamivir should be in 'adults'.

The Evaluation Center had the necessary amendments made to the Precautions and Warnings (draft).

2) Points of difference from the interpretation of the applicant

The Evaluation Center and Subcommittee do not accept the following interpretations from the applicant.

(1) In investigating the potential for bridging from the Phase III studies conducted overseas, that the distribution of zanamivir in the lungs was estimated to be the same level in Japan and overseas without any data; that they judged the differences between Japanese and foreign pharmacokinetics to have been individual variation; and that they inferred there to be no differences due to ethnic factors between Japan and overseas.

(2) In investigating the potential for bridging from the Phase III studies conducted overseas, that the three foreign studies (Europe, Australia and North America) were judged to be statistically combinable and the European and Australian data which did show significant difference in the major endpoint were combined with the North American data which had shown no significant difference; on top of this, that they concluded that the Japanese and foreign data were similar by an inappropriate statistical analysis technique and judged that there was reproducibility between the Japanese and foreign study findings.

(3) As the feature of this drug, that they claim 'Relenza is a revolutionary drug exhibiting anti-Influenza virus activity'; also that they claim that zanamivir can be anticipated to be effective in high risk patients and against Influenza B despite the fact that there is little clinical experience of it in Japan.

The Evaluation Center and Subcommittee believe that there are problems in respect of the following points.

(1) In the Japanese early Phase II study, no significant difference in efficacy was found between the zanamivir inhalation-only and combined inhalation and intranasal administration groups and the placebo group, nor was any significant difference in efficacy found in the Japanese late Phase II

study between the high dose and low dose zanamivir inhalation groups and the placebo group and there is a possibility that the optimum method of administration and dose level for the drug have not been determined.

(2)

From the data presented on this occasion, there is doubt as to whether or not zanamivir reaches the active site properly upon being inhaled.

2. Results of documentary compliance survey by Drugs Organization and Evaluation Center decision

1) Decision of Evaluation Center on documentary compliance survey

As a result of conducting a review with the documentation prescribed in Article 14 of the Pharmaceutical Affairs Law, we believe that apart from some non-compliances (Note), the standards laid down in Article 18-4-3 of the Pharmaceutical Affairs Law Enforcement Regulations have been met (reliability standards for application data).

(Note) Deviations from protocol, figures omissions in application data etc.

We accept the report of the data compliance survey result given by the Drugs Organization and have judged that there is no impediment to conducting the review based on the approved review data.

2) Decision of Evaluation Center regarding GCP survey

As a result of GCP review, the clinical studies conducted overseas were deemed to be 'compliant' but those conducted in Japan to be 'partially non-compliant'. The Evaluation Center judged that review could proceed based on approved application data from which some cases in the Japanese trials deemed to have 'GCP infringements' have been removed.

3. Review Result

The Evaluation Center believes that although the efficacy of zanamivir has been verified in Europe and the southern hemisphere in the data submitted, the currently submitted Japanese data are insufficient to permit bridging to the foreign data and at the present time, it is difficult for the Evaluation Center to judge the efficacy of zanamivir in Japan. Moreover, the GCP survey indicated that the Japanese trials were 'partially non-GCP compliant'. We believe it will be necessary to conduct appropriate an clinical trial adhering to GCP in an additional Japanese trial sought by the Subcommittee.