NIHS 2492

27th April, 2001

To the Director-General, Pharmaceutical Bureau,
Ministry of Health, Labour and Welfare

The Director of the National Institute of Health Sciences

Evaluation Report

This is to report the outcome of the evaluation of the approval application of the drug by the Pharmaceuticals and Medical Devices Evaluation Centre.

[Product Name]: Imigran Tablet 50

[Non-proprietary Name]: Sumatriptan succinate

[Name of Active Ingredients]: Sumatriptan succinate

[Applicant]: Glaxo SmithKline KK
(at the filing, it was GlaxoWellcome KK)

[Submission Date]: 2nd August 2000 (a manufacturing approval application)

[Dosage Form and Contents]: The Imigran Tablet 50 is presented as film-coated tablets, each tablet containing 70 mg of sumatriptan succinate (equivalent to 50mg of sumatriptan).

[Chemical Structure]

Omitted

Chemical name: 3-[2-(dimethylamino)ethyl]-N-methylindole-5-methanesulfonamide monosuccinate

[Evaluated by]: Evaluation Division II

Outcome of the Evaluation

27th April, 2001

[Product Name]:	Imigran Tablet 50
[Non-proprietary Name]:	Sumatriptan succinate
[Name of Active Ingredients]:	Sumatriptan succinate
[Applicant]:	Glaxo SmithKline KK (at the filing, it was GlaxoWellcome KK)
[Submission Date]:	2nd August 2000 (a manufacturing approval application)
[Dosage Form and Contents]:	The Imigran Tablet 50 is presented as film-coated tablets, each tablet containing 70 mg of sumatriptan succinate (equivalent to 50mg of sumatriptan).

[Outcome of the Evaluation]

The extrinsic ethnic factors of migraine in the Japanese and western populations do not differ particularly and pharmacokinetics of the Imigran Tablet 50 in the Japanese and western populations are similar. Therefore, a dose response study (placebo, 50mg and 100mg) was carried out in Japan as a bridging study in order to form a bridge with an existing overseas dose response study (placebo, 25mg, 50mg and 100mg). The result showed that the primary endpoint, headache response 4 hours after dosing, was significantly higher in the 50mg and 100mg groups compared with the placebo groups in both studies and their dose responses were similar. Furthermore, there were no major issues concerning the safety, and the types and the incidences of adverse events observed were similar in both studies. Therefore, bridging was considered to be successful. Based on the efficacy and safety, the recommended clinical dose was set at 50mg. The overseas' phase III study, which was extrapolated, was a placebo controlled investigation of efficacy and safety of 50mg sumatriptan when it was used for more than one attack. Headache response 4 hours after dosing was significantly higher than the placebo and there was no safety issue. The response rate in recurrent headache occurring 4 to 24 hours after the initial dose was significantly higher compared to placebo at 4 hours post-dose. In addition, there was no safety issue.

As a result of the above evaluation by the Pharmaceutical and Medical Devices Evaluation Centre, the Imigran Tablet 50 was judged as approvable with the following Indications and Dosage and Administration and recommended for discussion by the first committee on drugs.

[Indications]: Migraine
[Dosage and Administration]: Usually in adults, when experiencing a migraine headache, 50mg/dose of sumatriptan should be taken orally.
Depending on the condition, the dose may be increased to 100mg/dose. An additional dose of sumatriptan may be taken for a recurrence of migraine after successful treatment or if the initial treatment is not satisfactory. However, the additional dose should be at least two hours after the initial treatment and the total daily dose should not exceed 200mg.

Evaluation Report (1)

15th March, 2001

1. Outline of the Product

[Product Name]: Imigran Tablet 50

[Non-proprietary Name]: Sumatriptan succinate

[Submission Date]: 2nd August 2000 (a manufacturing approval application)

[Applicant]: Glaxo SmithKline KK
(at the filing, it was GlaxoWellcome KK)

[Dosage Form and Contents]: The Imigran Tablet 50 is presented as film-coated tablets, each tablet containing 70 mg of sumatriptan succinate (equivalent to 50mg of sumatriptan).

[Indications]: Migraine

[Dosage and Administration]: Usually in adults, when experiencing a migraine headache, 50mg/dose of sumatriptan should be taken orally. Depending on the condition, the dose may be increased to 100mg/dose.
An additional dose of sumatriptan may be taken if migraine recurs within 24 hours of successful treatment. However, the additional dose should be at least two hours after the initial treatment and the total daily dose should not exceed 200mg.

2. Summary of Submitted Documents and Evaluation by the Evaluation Centre

A. Data on Origin, Details of Discovery, Use in Foreign Countries, etc.

Migraine is a form of vascular headache. Typically, a patient experiences one or two attacks per month and an attack of severe throbbing pain will continue for several hours to several days. It often accompanies associated symptoms such as nausea, vomiting, photophobia and phonophobia. Some patients may experience prodromes, such as yawning, irritation and hunger on one or two days before the attack, or attacks may be associated with an aura, such as visual or sensual abnormalities including teichopsia, which occurs immediately before the attack. According to a national survey by Sakai, et al, (Cephalalgia 17:15-22, 1997) the prevalence of migraine is 8.4% of the population.

Pathology of migraine is not very well understood. Involvement of seretonine (5-hydroxytryptamine, hereinafter referred to as 5-HT) is believed to be important, as 5-HT is involved directly or indirectly in constriction and dilation of the cerebral blood vessels, and changes in the cerebral blood flow and a reduction in the platelet 5-HT concentration are observed during migraine attacks. Traditionally, ergotamine tartrate, which has a vasoconstrictive action, has been used as a treatment of an acute stage of migraine attacks. Although ergotamine is effective when it is administered up on early signs of migraine, administration after a headache has manifested does not provide sufficient relief. It is also known that ergotamine has effects on receptors other than 5-HT receptors such as adrenaline α, dopamine and muscarine receptors and constricts the peripheral vascular system as well as the cerebral blood vessels, thus it affects the circulation system, for example, increasing the blood pressure and reducing heart rate.

Sumatriptan succinate (hereinafter referred to as sumatriptan) has been developed by GlaxoWellcome in the UK as a treatment of migraine which selectively agonises a subtype of 5-HT receptor, 5-$HT_{1B/1D}$ receptor. In Japan, a subcutaneous injection of sumatriptan (the product name: Imigran Injection 3) was approved on 18th Jan. 2000 with indications for migraine and cluster headache. With injections, patients need to visit medical facilities when a prodromes/aura or attack is developing. Although tablets are less fast-acting compared with injections and the use may be limited in case of a migraine attack accompanying nausea or vomit, there is an advantage that patients can take a tablet without visiting medical facilities at the time of an attack as long as the patients have been diagnosed and prescribed with the drug. In Japan, the tablet formulation was developed parallel to the injections and approval applications for manufacturing and import of the tablet formulation were submitted together with those for the injection in (month) (year) by the former Japan Glaxo KK. However, the former second committee on drugs instructed, " the dose-response demonstrated in the phase II b dose response study is not clear and does not provide a sufficient justification for the dose amount of the tablet form. Implement the study again with clearer assessment criteria." As it would take long-time to repeat the study and also the recommended dose of the tablet formulation abroad was changing, the application for the tablet formulation was withdrawn on (month), (year). Since then, according to the ICH E5 guideline which was

under discussion at the time, the Japanese dose-response study (a repeated study) was positioned as a bridging study for the overseas' dose response study (Study S2CM09) and extrapolation was proved possible. Following the confirmation, the phase III study implemented aboard was extrapolated to the Japanese population and the resulting complete clinical data package was submitted with this application.

The migraine classification and diagnostic criteria, which were presented in the international headache society in 1988 (Cephalalgia 8 (Suppl 7): 9, 12-17, 19-73, 75-92, 1988), are widely used in Japan and abroad. It classifies migraine into 7 categories; (1) migraine without aura, (2) migraine with aura, (3) opthalmoplegic migraine (4) retinal migraine, (5) childhood periodic syndromes, (6) complications of migraine (status migrainous, migraineous infarction) and (7) migrainous disorder not fulfilling above criteria. The clinical studies included in this application have targeted migraine in the above categories (1) migraine without aura and (2) migraine with aura.

The tablet forms of sumatriptan have been approved in 113 countries including New Zealand as of January 2001. The nasal spray formulations have been approved in 48 countries. In Japan, development of the nasal spray has started in (year) and xxxxxxxxxx.

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

The Imigran Table 50 contains 70mg of the drug substance, sumatriptan succinate (3-[2-(dimethylamino)ethyl])-N-methylindole-5-methanesulfonamide monosuccinate) per tablet (equivalent to 50mg of sumatriptan). A subcutaneous formulation of sumatriptan has been approved on 18th January 2000. This is a new application of a tablet formulation. In order to make the tablets easy to swallow, the filed tablet formulation is altered and they are smaller than 50mg tablets that are commercially available in overseas countries.

The Characteristics, Identifications, Content Uniformity Test, Dissolution Test and Content (liquid chromatography) are established as the specification tests of the tablet

formulation. The specification and test methods of the standard sumatriptan succinate were also updated.

The Evaluation Centre requested the applicant to explain the reasons for each formulation change of the 50mg tablets (two types) used for development, the 50mg tablets used for launch abroad and the 50mg tablets for this application. The applicant responded that the components of the film-coating were changed in order to improve the appearance and the manufacturing process during the development, the colouring agents were added to the film-coating to differentiate the drug at the launch abroad and the compositions of the core and the film-coating were altered for this application in order to make the tablets smaller and so easier to swallow. The Evaluation Centre accepted the response. Equivalence of dissolution of those formulations has been confirmed in the dissolution tests and bioequivalence of the overseas marketed tablets and the filed tablets has been confirmed in the bioequivalence study abroad (see Section F).

The Evaluation Centre asked the applicant to review the specification of the dissolution test based on the actual values. The specification was changed appropriately and the specification was accepted. The Evaluation Centre also asked for details of the assessment of intermediate precision of the assays. The applicant these submitted the study results and the Evaluation Centre accepted these after checking the results.

Based on the above evaluation, the Evaluation Centre concluded that the properties and quality of the formulated product were analysed adequately and specifications and test methods were appropriate for maintaining constant quality.

C. Data on Stability

A long-term stability test at 25°C, 60% RH in dark of the final pack (blister packs) of the filed drug product has been carried out (still on-going). Results up to 12 months did not show any time-changes in any of the parameters and it was stable. Based on the results up to 12 months of the long-term stability test, the storage condition was set with a provisional shelf life of 1 year in airtight containers.

D. Data on Acute Toxicity, Semi-Acute Toxicity, Chronic Toxicity, Mutagenicity and other Toxicities

The single dose toxicity studies were carried out in rats and dogs. The approximate lethal oral dose was over 2,100mg/kg in male and female rats and over 500mg/kg in male dogs.

The repeated dose toxicity studies were carried out in rats and dogs receiving oral doses. Major toxicity findings were inanimation, abnormal phonation and muscle tone in rats and abnormal gait and a suppression of weight-gain in dogs, although all of them showed recovery. The no-toxicity doses were 50mg/kg/day (the 5 and 60-week studies) or 5 mg/kg/day (the 78-week study) in male and female rats and 10mg/kg/day (the 5, 26 and 60-week studies) in male and female dogs. Pharmacokinetic parameters after repeated oral dose were 120 to 300ng/mL (serum concentration at 1 hour post-dose) at 5mg/kg/day in the 78-week rat study and 1,100 to 1,700ng/mL (plasma concentration at 2 hours post-dose) at 10mg/kg/day in the 60-week dog study.

The reproductive toxicity studies were conducted in rats and rabbits receiving oral doses.

In the study of fertility and early embryonic development to implantation in rats, parent animals showed ptosis and increased food consumption, which were thought to have been caused by the pharmacological action, but no effects on fertility and early embryonic development were suspected. The no-toxicity dose for general toxicity and fertility of the parent animals and the next generation was estimated at 1,000mg/kg/day.

In the foetal organogenesis study in rats, dams showed flushed ears and limbs, which was thought to have been caused by the pharmacological action, but embryo lethality and teratogenicity were not suspected. The no-toxicity dose for general toxicity and fertility of the dams and the next generation was estimated at 1,000 mg/kg/day.

In the foetal organogenesis study in rabbits, dams showed variation in the body-weight increases and the food consumption. Furthermore, the F_1 foetus showed increased

incidences of angioplany in the neck and the chest and skeletal variations. The no-toxicity dose for general toxicity of dams was estimated at 15mg/kg/day, for fertility, 50mg/kg/day and for the next generation, 15mg/kg/day.

The peri- and post-natal study in rats showed decreases in body weight gain and food consumption in dams. As an effect on the F_1 generation, a reduction of the body weight was observed. The reductions in the birth index, the survival rate at day 4 and the weaning index observed at 1,000mg/kg/day were explained as unlikely to have toxicological significance. In dams, the no-toxicity dose for general toxicity was estimated at 10mg/kg/day and that for fertility was estimated at 1,000mg/kg/day. In the F_1 generation, that for general toxicity was estimated at 10mg/kg/day and for fertility, 1,000mg/kg/day and in the F_2 generation it was estimated at 1,000mg/kg/day.

The Evaluation Centre requested the applicant to provide discussion on relevancy of sumatriptan to the reduction in the birth rate, 4-day survival rate and weaning index observed in the rat peri- and post-natal study. The applicant responded by amending the no-toxicity dose for fertility of dams from 1000mg/kg/day to 100mg/kg/day. The Evaluation Centre accepted the change.

The Evaluation Centre asked for explanation on the safety of impurities. The applicant replied that as the result of assessment of data from general toxicity and genetic toxicity studies of sumatriptan and the amount of impurities, they believed there were no safety issues within the specifications. The Evaluation Centre accepted the reply.

E. Data on Pharmacology

As this is a supplemental application of a new administration route, no new additional study was conducted and submitted with the application. However, 11 published papers concerning comparison with similar drugs were submitted as references.

According to the past approval data concerning oral dose, accumulative intraduodenum administration of 100 to 10,000μg/kg sumatriptan increased the carotid resistance of

anaesthetised dogs dose-dependently, demonstrating similar pharmacological actions to subcutaneous and intravenous dosing.

According to reference data filed with this application, binding affinity to 5-HT_1 of sumatriptan was similar to eletriptan, zolmitriptan, naratriptan and rizatriptan and more selective to the human 5-HT_{1B}, 5-HT_{1D} and 5-HT_{1F}, compared with 5-HT_{1A} and 5-HT_{1E}. These drugs all demonstrated concentration-dependent constriction of the isolated cerebral arteries of humans, monkeys, dogs and rabbits. It has been reported that these drugs, including sumatriptan, also showed constrictive actions of the isolated human coronary artery, and the maximum reaction was about 20% of the maximum constriction caused by 5-HT.

The Evaluation Centre requested the applicant to provide a discussion on the effective plasma concentration in anaesthetised dogs including a comparison of intra-duodenum dosing and subcutaneous dosing. The applicant responded that the increases in carotid resistance were observed above 100μg/kg of intra-duodenum administration and above 30μg/kg of subcutaneous administration. Based on the maximum plasma concentrations (C_{max}) observed in the single dose (oral and subcutaneous) pharmacokinetic studies in dogs, the plasma concentration after intra-duodenum dosing (100μg/kg) and after subcutaneous dosing (30μg/kg) was estimated at approximately 33ng/mL and 36mg/mL, respectively, showing similar plasma concentrations. The applicant also pointed out that those concentrations were approximate to the C_{max} values (32.6ng/mL after p.o and 44.0ng/mL after s.c) observed with clinical dose in healthy adults (50mg p.o. and 3mg s.c.).

F. Data on Absorption, Distribution, Metabolism and Excretion

Results in Animals

Absorption, distribution, metabolism and excretion of an oral dose of ^{14}C-labelled sumatriptan succinate or unlabelled sumatriptan succinate were investigated in rats and dogs. The rats and dogs received sumatriptan succinate administration equivalent to 2mg/kg of sumatriptan.

Absorption: When rats received an oral dose of ^{14}C-sumatriptan succinate or the unlabelled sumatriptan succinate, plasma radioactivity and unchanged sumatriptan both reached C_{max} at 2 hours after the administration and eliminated with a half-life ($t_{1/2}$) of 1 to 3 hours. As the concentration of unchanged sumatriptan was lower than the radioactivity from an early stage, a presence of the first pass effect was suggested. In a dose range up to 8 mg/kg, near linearity was observed between the dosed amount and the C_{max} of plasma radioactivity and the area under plasma concentration – time curve (AUC). When dogs received an oral dose, the plasma radioactivity and unchanged sumatriptan levels reached C_{max} within an hour of administration then eliminated at $t_{1/2}$ of approximately 2 hours, suggesting the presence of the first pass effect, in a similar way to rats. There were not sex differences in plasma radioactivity profiles in rats and dogs.

When rats received repeated doses once daily for 21 days, $AUC_{0\text{-}24hr}$ after dosing was increased with dosing. After the 21st administration, $AUC_{0\text{-}8}$ was approximately three times higher than after the initial administration. The $t_{1/2}$ was stayed similar after the 7th administration. Plasma radioactivity was increased with dosing, but after the third administration, it remained roughly within a specific range.

The absorption rate of radioactivity after oral dose of ^{14}C-sumatriptan succinate was approximately 76% in rats and 69% in dogs. When rats received an oral dose with or without food, C_{max} of fasting animals was 1.6 times of fed animals and $t_{1/2}$ was 0.40 times and AUC was roughly the same. Sumatriptan was believed to be absorbed throughout the small intestine and absorption was better at lower small intestine.

Distribution: When rats received an oral dose of ^{14}C-sumatriptan succinate, the majority of tissues showed the maximum radioactivity at 2 hours after the administration. At 2 hours post-dose, radioactivity in the ileum and the liver were highest, but at 168 hours after administration, radioactivity had disappeared from most of the tissue showing no specific organs with the residue. When rats received repeated doses, organ and tissue concentrations at 24 hours post-dose increased with daily dose and by the 21st

administration, the majority of tissues nearly reached the steady state. However, distribution in the tissues did not show marked differences from single dose findings.

When ^{14}C-sumatriptan succinate was administered to rats on day 12 or day 18 of pregnancy, transmigration to the placenta and foetuses was observed, but little was believed to have remained.

The plasma protein binding rate in rats, dogs and humans are 24 to 34% *in vitro* and a trend of strong binding to specific human plasma protein was not observed. The haemocyte-binding rate was believed to be 60 to 71% regardless of animal species and time after dosing.

Metabolism: The majority of orally administered sumatriptan succinate received oxidative deamination and N-demethylation to produce an indoleacetylated metabolite and a N-demethylated metabolite, respectively. The main metabolites in rats were believed to be an indoleacetylated metabolite and a N-demathylated metabolite, and in dogs, an indoleacetylated metabolite. In rats and dogs, there was no sex difference in metabolites in the urine and the faeces and glucuronate conjugate and sulfate conjugate were considered to be absent. It was suggested that the involvement of P450 in sumatriptan metabolism was minimal and monoamine oxidase A (MAO-A) was believed to be mainly responsible.

Excretion: When rats and dogs received oral dose of ^{14}C-sumatriptan succinate, respectively, 45% to 58% and 68% to 81% of the dosed radioactivity was excreted in the urine and, respectively, 29% to 41% and 9% to 12% in the faeces by 168 hours after dosing. There was no change in the elimination rates after repeated doses compared with a single dose. The elimination rate in the bile up to 24 hours post-dose was low; approximately 8% of the dosed amount in rats and approximately 2% in dogs, suggesting the bile was not the main route of elimination. When ^{14}C-sumatriptan succinate was orally administered to weaning rats, radioactivity in the milk reached the maximum level at 4 hours after the administration and showed high transmigration reaching 4 to 15 times of plasma radioactivity by 8-hours post-dose. However, it was eliminated at

similar $t_{1/2}$ as the plasma radioactivity and it was below the detection limit at 48 hours post-dose.

Results in Humans

Plasma Concentration: When 16 healthy adult male volunteers received a single dose of 50mg and 100mg sumatriptan after fasting, plasma unchanged sumatriptan concentration showed bimodality. The first peak was seen by 1.5 hours post-dose and the second peak was seen between 2 and 3 hours post-dose, then it was eliminated at $t_{1/2}$ of approximately 2 hours. C_{max} and AUC_{0-8} were increased with increases in the dosed amount. In a single dose study in 6 healthy adult male volunteers who orally received 25mg, 50mg and 100mg of sumatriptan after fasting, C_{max} and AUC_{0-12} were also increased with increases in the dosed amount.

When 6 healthy adult male volunteers received an oral repeated dose of 50mg and 100mg of sumatriptan once daily for 5 days, plasma unchanged sumatriptan concentrations showed similar profiles on the first day and the fifth day, showing no large differences in any of pharmacokinetic parameters.

When 12 healthy adult male volunteers received a single oral dose of 200mg sumatriptan after a meal, t_{max} was 2.25 hr (range: 1.50 to 3.50hr) showing a tendency of delay compared with a dose after fasting (1.75hr, range: 0.75 to 3.52hr). However, C_{max} $t_{1/2}$ and AUC_{0-8} showed no differences.

The bimodality of the plasma concentration profile was discussed from the absorption process of sumatriptan and enterohepatic circulation. When healthy adult male volunteers received oral, intrajejunum and intraduodenum administration, absorption of an oral dose and an intrajejunum dose were similar, suggesting possible absorption from the small intestine (Pharm Res 12(1): 138-143, 1995). It was also suggested that sumatriptan was absorbed by whole region of the small intestine in rats and absorption at lower regions were better (see Results in Animals, Absorption). As excretion in the bile was poor in animals, the main metabolite in humans was not glucuronate conjugate and a subcutaneous dose in humans did not show bimodality of the plasma concentration

profile, the applicant argued that bimodality after an oral dose was not due to enterohepatic circulation. They concluded that after an oral dose in humans, continuous absorption by the whole region of the small intestine was observed from 30 minutes post-dose till 3 hours post-dose then the second peak appeared at around 3 hours post-dose, due to absorption from the lower region of the small intestine.

Metabolism: The main metabolic pathway in humans was suggested to be the production of the indoleacetylated metabolite through oxidative deamination followed by glucuronidation.

Excretion: The rate of excretion of unchanged sumatriptan and the indoleacetylated metabolite via urine after a single oral dose of 50mg and 100mg of sumatriptan in 16 fasting health adult male volunteers was approximately 2% and 40% of the dosed amount at 24 hours post-dose at both dose levels, showing no difference with the dosed amount. Repeated administration (50mg and 100mg orally once daily for 5 days, n=6) also did not show a change in elimination.

Interactions: When healthy adult male volunteers received an oral dose of sumatriptan after orally taking propranolol (a β blocker), flunarizine (a Ca antagonist) or alcohol, no change in pharmacokinetics of sumatriptan was observed. When healthy adult male and female volunteers received an oral dose of sumatriptan after an oral dose of moclobemide (a MAO-A inhibitor), 4.4-fold increase in AUC_{0-8}, 2.6-fold increase in C_{max} and 1.4-fold increase in $t_{1/2}$ of sumatriptan were observed. When healthy adult females received a subcutaneous sumatriptan injection after oral administration of selegiline (a MAO-B inhibitor), no effect on pharmacokinetics of sumatriptan was observed.

Investigation in Patients with Hepatic Impairment: To 8 patients with mild hepatic impairment, a single oral dose of 50mg sumatriptan was given. Their plasma unchanged sumatriptan levels were higher than the levels seen in 8 healthy adults and their C_{max} and AUC_{0-8} were about 1.8 times higher than those of healthy adults. However, this study did not show adverse events specific to these subjects or serious adverse events. A study in Japanese and overseas healthy adult male volunteers who orally received 100mg and

400mg of sumatriptan, respectively, demonstrated good tolerability. Therefore, no dose adjustment for migraine patients with hepatic function impairment was believed to be required, but it should be administered with care as the blood concentration may increase. Also, it was contraindicated to patients with serious hepatic function impairment.

Comparison of pharmacokinetics of the Japanese and overseas populations: In Japanese and overseas healthy adult male volunteers, plasma unchanged sumatriptan concentration profiles after a single oral dose of 50 mg sumatriptan were similar. Also, pharmacokinetic parameters and urine elimination rates did not show a marked difference between the races. With a single oral dose of 50mg and 100mg sumatriptan, both the Japanese and overseas populations demonstrated an increase correlating with the dosed amount, indicating no difference in pharmacokinetics between the Japanese and overseas populations.

Bioequivalence

In Japanese clinical studies, 50 mg tablets (50mg A tablet, the filed tablet) were used, but in overseas clinical studies, three different types of 50mg tablets (50mgB tablet, 50mgC tablet and 50mgD tablet (the overseas commercial formulation)), as well as 25mg tablets and 100mg tablets were used. The results of dissolution tests showed that although tablets used in Japanese and overseas clinical studies (25mg, 50mgA, 50mgB, 50mgC, 50mgD and 100mg tablets) differed in compositions, their dissolution rates at 15 minutes were almost 100%, showing no difference in dissolution behaviour. The results of a bioequivalence study abroad showed that tablets used in the Japanese clinical studies (50mgA) and the overseas clinical studies (50mgD) were biologically equivalent.

Various reviews (Lancet 341:221-224, 1993, Lancet 355: 860-861, 2000) state that bioavailability (BA) of oral sumatriptan was low and the effect was weaker than other triptans. Therefore, the Evaluation Centre requested an explanation on BA in humans and a view on developing an oral formulation. The applicant indicated that bioavailability in healthy adult male volunteers was approximately 14%, which was lower than other triptans (approx. between 40 and 70%). They believed that this was due to

the first pass effect because subcutaneous administration showed a high absolute bioavailability. They also stated that while the t_{max}, protein binding rate, distribution area and clearance did not show marked difference from other triptans, the lipid solubility was lower than other triptans. With regard to the weak effect of sumatriptan compared with other triptans mentioned in Lancet, the applicant illustrated that, when looking at the "response at 2 hours post-dose," which was the primary endpoint of these comparative studies, as with other triptans, sumatriptan showed a significantly higher rate than the placebo and the response was similar to all other triptans apart from 80 mg rizatriptan. They also pointed out that the comparative studies with rizatriptan and eletriptan (Arch Neurology 53: 1132-1137, 1996, Neurology 54: 156-163, 2000) used sumatriptan tablets in capsules. As it was suggested that putting a drug in capsules delayed its absorption, they argued, the assessment at 2 hours after dosing in those comparative studies did not reflect the true response of sumatriptan. Also, with regard to zolmitriptan, they presented a paper (Drugs 58 (2): 347-374, 1999) reporting no difference in efficacy of zolmitriptan and sumatriptan. They explained that there was a report in JAMA stating, "although there are slight differences in pharmacokinetic characteristics such as absorption, $t_{1/2}$ and plasma concentration, differences in efficacy and safety among triptans are between 5 and 10%" (JAMA 280 (23): 1975-1976, 1998). The Evaluation Centre accepted the responses.

The Evaluation Centre instructed the applicant to present pharmacokinetic parameters and blood concentration profiles in patients between attacks and during an attack and discuss the relationship of the blood concentration and time to effect to appear. The applicant presented serum concentration profiles in a single oral study (Study S2B206) in migraine patients who received 25mg, 50mg and 100mg between attacks and during an attack. While administrations between attacks and during an attack both showed increases in C_{max} and AUC_{4h} following increases in the dosed amount, average serum concentrations up to 2 hours after a dose of 50mg and 100mg during an attack tended to be lower, and when 25mg was administered between attacks and during an attack, statistically significant differences in their AUC_{4h} and T_{max} were observed. However, they explained, in the above Study S2B206, sumatriptan groups showed statistically significant superior headache relief at 2 hours and 4 hours after administration compared

with the placebo. Furthermore, reductions in the blood concentrations were reported with other triptans when they were administered during an attack. This was explained with possible gastric stasis or delay in gastric emptying (Cephalalgia 16: 270-275, 1996, Neurology 50 (Suppl. 4): A377, 1998). The Evaluation Centre considers these responses are acceptable, but would like to refer to the Expert Review.

The Evaluation Centre asked the applicant to submit pharmacokinetic data when humans received 100mg or over and to discuss the linearity, as Japanese migraine patient studies did not provide data on 100mg taken twice with a short interval, despite it being likely to happen, and also because C_{max} and AUC in Japanese patients were higher than western patients. The applicant submitted serum concentration profiles and pharmacokinetic parameters when overseas healthy adult male volunteers received a single oral dose of 100mg, 200mg, 300mg and 400mg sumatriptan (n=15, 15, 14 and 14, respectively). Their C_{max} and AUC_{0-8} were increased proportionally to the dosed amount and linearity was shown in a range between 100mg and 400mg. They explained that at any dose level, good tolerability was observed. They also argued that there were no fundamental differences in pharmacokinetic parameters between the Japanese and overseas populations. The Evaluation Centre accepted the response.

The Evaluation Centre requested that the applicant provide an explanation of the possibility of sex differences in plasma concentration profiles of humans, as oral doses in dogs demonstrated different plasma concentration profiles up to 1 hour after dosing in male and female animals. The applicant replied that a comparison of female and male plasma radioactivity and pharmacokinetic parameters at various time-points up to 1 hour post-dose in dogs using the Student t test showed no significant differences ($p<0.05$). They also argued that, in humans, although AUC_{0-8} in females (n=18) was higher (21%) than that in males (n=18), other parameters did not show sex differences, therefore, there was no clinically significant sex difference. The Evaluation Centre accepted the response.

G. Data on Clinical Study Results

G-1 Summary of Submitted Data

Clinical investigations of sumatriptan were conducted in phase I to phase III studies between (year) to (year) by Japan Glaxo KK. On (day), (month), (year), applications for manufacturing and import were submitted, but in the meetings of the 2nd Committee on New Drugs held on (day), (month), (year) and (day), (month), (year), the applicant was instructed to submit study data supporting the dose selection, as the dose response had not been clearly demonstrated. The applicant positioned the dose- response study, which was going to be repeated in Japan, as a bridging study of the dose-response study (Study S2CM09) that had been implemented abroad and carried out the study using the same study design and assessment criteria as the study S2CM09. As a result, the recommended dose in Japan was set at the same dose as abroad, 50mg. Furthermore, because efficacy and safety in this study showed similarities to efficacy and safety seen in the study S2CM09, the overseas phase III placebo controlled comparative study of 50mg sumatriptan tablets (Study S2CM07) was extrapolated as a phase III clinical study in Japan and was submitted as the evaluation data.

Consequently, the following studies were submitted with this application as the evaluation data.

Phase I Studies

- Single dose and repeated dose studies (Study AM-1 and Study AM-2): Investigations of pharmacokinetics and safety in healthy adult male volunteers
- Pharmacokinetic studies (Study SUM-PK001 and Study SUM40036): Investigations of pharmacokinetics in Japanese and overseas healthy adult male volunteers

Phase II Dose-Response Studies

- A dose-response study (Study GW102-201): A bridging study of a dose-response study implemented abroad (Study S2CM09)
- A dose-response study implemented abroad (Study S2CM09): A placebo-controlled double-blind dose-response study implemented abroad

Phase III Comparative Study

- A placebo-controlled double-blind comparison study with a parallel-groups design implemented abroad (Study S2CM07)

Excluding the phase I studies, results of the clinical studies that had been used in the previous application in (year) were submitted as reference data, as those studies employed different evaluation methods of efficacy (headache response) and safety from those used in the newly implemented phase II dose-response study (Study GW102-201) and overseas clinical studies (Study S2CM07 and Study S2CM09). In these reference studies, no standardised assessment criteria for evaluation of headache response were employed and safety was not assessed with adverse events, but assessed only with adverse drug reactions.

(1) Phase I Clinical Studies

1. Single-dose and repeated-dose studies

As 100mg was chosen as an optimum dose based on a dose selection study in migraine patients in the UK, 100mg was used as the highest dose in the single-dose study and 3 escalating doses of 25, 50 and 100mg were administered to 6 subjects. Based on the results of the single-dose study, 2 dose levels of 50 and 100mg were used in the repeated oral dose study and 8 subjects were randomly allocated to the placebo group (2 subjects) or the sumatriptan group (6 subjects). The subjects received oral repeated dose of either a placebo or 50mg tablet once daily for 5 days after fasting. After 2 weeks of a wash-out period, the subjects were again randomly allocated to the placebo group (2 subjects) or the sumatriptan group (6 subjects) and received oral repeated doses of either a placebo or 100mg tablet once daily for 5 days after fasting.

In a single oral dose study, the subjects in the 25 and 50 mg groups presented no abnormal findings in any of the tests and observations that were thought to be caused by the drug, and no adverse drug reaction. One subject experienced head pressure and another subject experienced a heavy head when they received 100mg, but both were mild and transient. In the repeated oral dose study, the subjects in the 50mg group presented no abnormal findings in any of the tests and observations that were thought to be caused

by the drug, and no adverse drug reactions. In the 100mg group, however, a transient increase in the diastolic blood pressure on average 3 to 5 mmHg and an increase in AST (GOT) within the normal range (11.5 ±1.6U baseline to 17.0±3.0U 24 hours post-dose on Day 5) were observed.

2. Pharmacokinetic studies

The pharmacokinetic studies were implemented in order to compare pharmacokinetics in Japanese (16) and overseas (19) healthy adult male volunteers. In these studies, subjects received a single oral dose of 1 tablet (50mg), 2 tablets (100mg) or 1 overseas marketed tablet (50mg, the overseas subjects only) after fasting, in a cross-over fashion. No Japanese subjects presented abnormal findings in any of tests and observations that were thought to be caused by the drug or adverse drug reactions. Among the overseas subjects, 1 subject each in the 50mg group presented mild headache and lethargy, 1 subject who took an overseas marketed tablet presented mild lethargy and 1 subject in the 100mg group presented mild headache, but no other abnormal findings in tests and observations that were thought to be caused by the drug, and no other adverse drug reactions were observed (for the pharmacokinetic results of the studies, see Section F).

(2) Phase II Dose-Response Study (Study GW102-201)

Initially, the recommended dose in Europe was set at 100mg. In the USA, the recommended dose was 25mg with the maximum recommended dose of 100mg/dose. Subsequently, the recommended dose in Europe and the USA was unified to 50mg, based on a result of the large-scale dose-response study (Study S2CM09) conducted in Europe from (year) till (year). When a dose-response study was repeated in Japan using the same assessment criteria as abroad, the dose levels in the study were set at 50 and 100mg with the placebo as a control, as the applicant considered that 25mg would not provide a sufficient clinical response. The dose-response was investigated in the single oral dose double-blind comparison study with a parallel-group design.

The inclusion criteria were: 1) patients with migraine with or without aura according to the migraine diagnosis criteria of the international headache society for at least 6 months

prior to the study, 2) patients who have 1 to 6 migraine attacks which are severe (Grade 3) or moderate (Grade 2) in severity for at least 3 months prior to the study.

* Severity of headache was graded in the assessment criteria used abroad. There were 4 grades of Grade 0 (no pain), Grade 1 (mild – nascent - pain), Grade 2 (moderate – tolerable- pain) and Grade 3 (severe – intolerable - pain).

Two hundred and seventy four patients were enrolled in the study; and 43 patients who did not take the trial drug, 1 patient who violated the GCP, 1 patient who missed all observations after administration and 1 patient whose headaches usually lasted less than 4 hours were excluded from the analysis. As a result, the full analysis set (FAS) consisted of 228 patients (78 in the placebo group, 76 in the 50 mg group and 74 in the 100mg group).

A total of 19 patients; 7 who violated exclusion criteria, 7 who took additional analgesics within 4 hours of the trial drug administration, thus did not follow concomitant medication criteria, 3 with missing observation data at 4 hours after administration of the trial drug and 2 with organic brain diseases were excluded from FAS. The per protocol set (PPS) consisted of 209 patients (70 in the placebo group, 70 in the 50g group and 69 in the 100mg group). Two hundred and thirty, i.e., 231 who took drugs minus 1 GCP violation, were included in the safety analysis. It was predefined to have carried out the primary efficacy analysis in the PPS.

The patient background showed biases in “presence/absence of accompanying symptoms of migraine” and “history of treatment” ($p<0.15$) and the patient background at administration showed a bias in “presence/absence of phonophobia” ($p<0.15$). However, adjustments of those covariates did not have a large effect on the result.

The primary endpoint, the response rate shown as the percentage of patients with headache response (defined as a reduction in headache severity from severe (Grade 3) or moderate (Grade 2) pain to mild (Grade 1) or no pain (Grade 0)) at 4 hours after administration in the PPS, was 48.6% (34/70) in the placebo group, 71.4% (50/70) in the 50mg group and 66.7% (46/69) in the 100mg group. To assess dose-response of the response rate, the Cochran-Armitage test (contrast –1, 0, 1 and contrast 0, 1, 1) was

carried out. With each contrast, they showed significance (p=0.0138, p=0.0020, respectively) and the dose-response of the response rate was described as "the placebo group < the 50mg group = the 100mg group." The response rate of the 50 and 100mg groups were significantly higher than the placebo group (χ^2 test: p=0.0058, p=0.0309, respectively). In the FAS, the response rate was 47.4% (37/78) in the placebo group, 68.5%(50/73) in the 50mg group and 67.6% (50/74) in the 100mg group. An assessment of dose-response of the response rate with the Cochran-Armitage test (contrast –1, 0, 1 and contrast 0, 1, 1) showed significance with both contrasts (p=0.0052, p=0.0013) and dose-response of the response rate was described as "the placebo group < the 50mg group = the 100mg group." The response rate in the 50 and 100mg groups was significantly higher than the placebo group (χ^2 test: p=0.0089, p=0.0122, respectively).

The secondary endpoints, the response rates shown as the percentages of patients with headache response 0.5, 1, 2 and 3 hours after administration, did not show statistically significant difference in the 50mg and 100mg groups compared with the placebo group. With regard to the percentage of patients with no pain at 0.5, 1, 2, 3 and 4 hours after administration of the trial drug, there was no group difference up to 3 hours after administration. However, the rate of patients with no pain at 4 hours after administration was 24.3% (17/70) in the placebo group whereas it was 45.7% (32/70) in the 50mg group and 46.4% (32/69) in the 100mg group, showing significantly higher no pain rates in the 50 and 100mg groups compared with the placebo group (χ^2 test: p=0.0079, p=0.0064, respectively). The normalisation rate of clinical disability (defined as a percentage of patients whose disability rating was down to 0 (able to function as normal)) at 0.5, 1, 2, 3 and 4 hours after administration of the trial drug was increased with time for up to 3 hours after administration and there was no group difference in the normalisation rate at each time point. However, the normalisation rate 4 hours after administration was 35.7% (25/70) in the placebo group whereas it was 56.3% (36/64) in the 50mg group and 56.5% (39/69) in the 100mg group, showing a significantly higher normalisation rate in the 50 and 100mg groups compared with the placebo group (χ^2 test: p=0.0171, p=0.0139, respectively). Nausea dissipated with time in all groups and there was no significant difference in the percentage of patients without nausea in the

groups at any time-point. As few patients experienced vomiting at dosing, it was unable to assess the differences among the groups. Photophobia was dissipated with time for up to 4 hours after administration in the 50 and 100mg groups. The percentage of patients without photophobia at 2 and 4 hours after administration in the 50mg group were 68.6% (24/35) and 91.4% (32/35), respectively, which were significantly higher than the percentage at 2 and 4 hours after administration in the placebo group (39.4% (13/33) and 66.7% (22/33), respectively, χ^2 test at 2 hours after administration: p=0.0158, Fisher's exact probability test at 4 hours after administration: p=0.0162). With regard to phonophobia, there was no significant difference in the 50mg group compared to the placebo group for up to 3 hours after administration, however, the percentage of patients without phonophobia at 4 hours after administration was 86.8% (33/38), which was statistically higher than the percentage in the placebo group (62.8% (27/43), χ^2 test: p=0.0137). In the 100mg group, the percentage of patients without phonophobia at 2, 3 and 4 hours after administration were 76.9% (20/26), 92.9% (26/28) and 89.3% (25/28), which were significantly higher than the percentage at the respective time points in the placebo group (48.8% (21/43), 65.1% (25/38) and 62.8% (27/43), χ^2 test at 2 hours after administration: p=0.0213, χ^2 test at 3 hours after administration: p=0.0074, χ^2 test at 4 hours after administration: p=0.0137).

The incidences of adverse events were 48.7% (38/78) in the placebo group, 61.0% (47/77) in the 50mg group and 60.0% (45/75) in the 100mg group. The numbers of adverse events in the placebo, 50 and 100mg groups by their severity were 50, 75 and 67 mild, 12, 8 and 8 moderate and 1, 0 and 1 severe adverse events, respectively. One patient each in the placebo and 100mg groups reported worsening of migraine as a severe adverse event. With treatments such as administration of analgesics, these events dissipated 3 and 4 hours later, respectively. The incidences of adverse events that were not assessed as 'not relevant' to the trial drug (adverse drug reactions) were 19.2% (15/78) in the placebo group, 29.9% (23/77) in the 50mg group and 26.7% (20/75) in the 100mg group. Of those adverse drug reactions, palpitation (1 in the placebo group, 6 in the 50mg group and 1 in the 100mg group), chest pain (0 in the placebo group, 1 in the 50mg group and 2 in the 100mg group), malaise (0 in the placebo group, 4 in the 50mg group and 3 in the 100mg group) and weakness (0 in the placebo group, 1 in 50mg

group and 1 in 100mg group) were observed more in the sumatriptan groups than the placebo group and considered to be clinically significant.

Eight patients (10 events) in the placebo group, 11 patients (16 events) in the 50mg group and 6 patients (7 events) in the 100mg group had abnormal changes in lab test values. Of these, 4 patients (6 events) in the placebo group, 2 patients (3 events) in the 50mg group and 4 patients (5 events) in the 100mg group were considered to have had abnormal changes that were not assessed as 'not relevant' to the trial drugs. None of the abnormal changes could be described as large numerical deviations from the normal ranges and none of those test items were specifically considered to be clinically significant in the sumatriptan groups.

With regard to systolic pressure, diastolic pressure and the heart rate before and after administration, none of them showed significant changes.

(3) Dose-Response Study (Overseas Clinical Study, Study S2CM09)

This study was conducted in order to compare efficacy and safety of 25, 50 and 100mg sumatriptan for migraine with the placebo. To assess consistency of the effect on recurrent migraine attacks, administration of the trial drug in three separate migraine attacks was allowed in this study. The primary endpoint for efficacy was the response rate indicated as the percentage of patients with headache response 4 hours after administration at the first attack (a reduction in headache severity from severe (Grade 3) or moderate (Grade 2) pain to mild (Grade 1) or no pain (Grade 0)). Also, the efficacy on headaches recurring 4 to 24 hours after the administration of the trial drug was also assessed. When comparing the efficacy with the dose-response study conducted in Japan (Study GW102-201), data concerning efficacy of the first dose in this study were used and for a comparison of the safety, the adverse drug reactions seen with the initial administration in this study were used.

The inclusion criteria were: 1) patients with migraine with or without aura according to the migraine diagnosis criteria of the international headache society for at least 12

months prior to the study, 2) patients who have 1 to 6 migraine attacks which are severe (Grade 3) or moderate (Grade 2) in severity for at least 12 months prior to the study.

One thousand and fifty seven patients in total were enrolled to the study and of these, 1003 patients (99 in the placebo group, 303 in the 25 mg group, 303 in the 50mg group and 298 in the 100mg group) took the trial drug at at least 1 attack and they were all included in safety analysis. On the first attack, 1001 patients (98 in the placebo group, 303 in the 25mg group, 302 in the 50 mg group and 298 in the 100mg group) were included in the intent-to-treat (ITT) analysis and 719 patients (64 in the placebo group, 201 in the 25 mg group, 225 in the 50mg group and 229 in the 100mg group) were included in the per-protocol (PP) analysis, excluding 282 patients who were included in ITT analysis. The most common reason for excluding those patients was "took the trial drug, which should have been taken at recurrences, as an additional dose". The primary analysis was predefined as ITT analysis.

The primary endpoint, the response rate indicated as the percentage of patients with headache response 4 hours after administration at the first attack was 39% (34/87), 65% (167/258), 77% (199/258) and 77% (196/256) in the placebo, 25, 50 and 100mg groups, respectively. The response rates in the 25, 50 and 100mg groups were significantly higher than in the placebo group (Mantel-Haenszel χ^2 test; $p<0.001$ for all dose groups). The response rates in the 50 and 100mg groups were significantly higher than in 25mg group (Mantel-Haenszel χ^2 test; the 50mg group: $p=0.002$, the 100mg group: $p=0.003$).

The secondary endpoints, the headache response rates at the 2nd and 3rd attacks, were similar to the finding at the 1st attack. When looking at changes in the response rate as headache response at 0.5, 1, 2 and 3 hours after administration, the response rate in the 50 and 100mg groups at more than 0.5 hours after administration and in the 25 mg group at more than 1 hour after administration was statistically significantly higher than the placebo group. The percentage of patients with no pain 2 hours after administration of the trial drugs was 9% (8/89), 21% (55/265), 31% (84/274) and 35% (96/275) in the placebo, 25, 50 and the 100mg groups, respectively, showing significantly higher relief in the sumatriptan groups compared with the placebo group (Mantel-Haenszel χ^2 test; the

25mg group: p=0.012, the 50mg group: p<0.001, the 100mg group: p<0.001). The percentage of patients with no pain 4 hours after administration was 25% (22/87), 43% (110/258), 55% (142/258) and 58% (148/256) in the placebo, 25, 50 and 100mg groups, respectively, showing significantly higher relief in the sumatriptan groups compared with the placebo group (Mantel-Haenszel χ^2 test; the 25mg group: p=0.004, the 50mg group: p<0.001, the 100mg group: p<0.001). The percentage of patients with Grade 0 (able to function as normal) in the clinical disability 4 hours after administration was 29% (26/09), 49% (129/263), 57% (147/260) and 62% (165/268) in the placebo, 25, 50 and 100mg groups, respectively. With regard to nausea and photo/phonophobia, the 25, 50 and 100mg groups had a higher percentage of patients without those symptoms 4 hours after administration, compared with the placebo group. The percentage of patients who vomited was low in all groups including at administration.

The percentages of patients who experienced recurrence of headache 4 to 24 hours after the initial treatment among patients who responded to the treatment of the first attack at 4 hours after the treatment were 35% (12/34) in the placebo group, 34% (57/167) in the 25mg group, 34% (67/198) in the 50mg group and 30% (59/196) in the 100mg group, thus a similar percentage of patients experienced the recurrence in each group. The response rate for recurrent attack treatment when the placebo or 25, 50 or 100mg sumatriptan was administered up on the recurrent headache was higher in patients who took 25, 50 or 100mg sumatriptan than patients who took with the placebo.

Adverse events at the initial treatment were seen in 20.2% (20/99) of patients in the placebo group, 24.4% (74/303) in the 25mg group, 27.1% (82/303) in the 50mg group and 37.2% (111/298) in the 100mg group. The incidences of severe adverse events were 3.0% (3/99), 2.0% (6/303), 4.6% (14/303) and 5.0% (15/303) in the placebo, 25, 50 and 100mg groups, respectively.

The incidences of adverse event relevant to the trial drugs (adverse drug reactions) were 11.1% (11/99) in the placebo group, 17.2% (52/303) in the 25mg group, 20.8% (63/303) in the 50mg group and 31.2% (93/298) in the 100mg group.

The common adverse drug reactions (2% or more) were “headache NOS (not otherwise specified)”, “floating dizziness (excluding spinning vertigo)”, “spinning vertigo NEC (not elsewhere classified)”, “nausea and vomiting NOS” and “heavy feeling” in the placebo group, “heavy feeling”, “malaise and fatigue” and “hot feel” in the 25mg group, “paresthesia NEC”, “spinning vertigo NEC”, “chest pressure/chest pain NEC”, “nausea and vomiting NOS” and “malaise and fatigue” in the 50 mg group and “somnolence”, “floating dizziness (excluding spinning vertigo)”, “spinning vertigo NEC”, “nausea and vomiting NOS”, “chest pressure/chest pain NEC”, “dry mouth”, “musculoskeletal pain”, “heavy feeling”, “pressure NOS”, “malaise and fatigue” and “hot feeling” in the 100mg group.

Looking at adverse events of treatment of recurrent headache, the incidences of adverse events after administration of the trial drug to treat all three, the 1st to the 3rd migraine attacks or any of the recurrent attacks were 16.0% (8/49) in the placebo + 100mg group (patients in this group received the placebo on the first treatment and then a 100mg tablet for the following attacks; the same rules apply below), 17.1% (22/129) in the 25mg + 25mg group, 8.6% (10/116) in the 50mg + 50mg group, 19.8% (20/101) in the 100mg + 100mg group, 11.9% (8/67) in the 25mg + placebo group, 9.5% (6/63) in the 50mg + placebo group and 13.5% (7/52) in the 100mg + placebo group. The incidences of severe adverse events were 4.1% (2/49) in the placebo + 100mg group, 4.7% (6/129) in the 25mg + 25mg group, none in the 50mg + 50mg group, 3.0% (3/101) in the 100mg + 100mg group, 1.5% (1/67) in the 25mg + placebo group, none in the 50mg + placebo group and 3.8% (2/52) in the 100mg + placebo group. Adverse events relevant to the trial drugs (adverse drug reactions) that were reported more than twice were “chest pain” and “malaise and fatigue” in the placebo + 100mg group, “nausea and vomiting NOS” and “high blood pressure NOS” in the 25mg + 25mg group, “nausea and vomiting NOS”, “heavy feeling” in the 50 mg + 50mg group and “chest pressure/chest pain NEC” in the 100mg + 100mg group.

Five patients experienced one serious adverse event each of urinary calculus, headache NOS, convolution NOS, chest pain NEC and musculoskeletal pain. The investigators assessed all of these “not relevant” or “unlikely to be relevant” to the trial drug.

Fifteen patients were withdrawn from the study due to the adverse events. Although 2 of them (chest pain NEC and musculoskeletal pain) fulfilled criteria of serious adverse events, the investigator assessed one of them "not relevant" to the trial drug and the other "unlikely to be relevant" to the trial drug.

(4) Phase III Comparative Study (Overseas Clinical Study, Study S2CM07)

This study was implemented in order to compare efficacy and safety of 50mg sumatriptan for migraine with placebo. To assess consistency of the efficacy on recurrent migraine attacks, administration of the trial drug in 3 separate migraine attacks was allowed in this study.

The inclusion criteria were the same as the study S2CM09.

Five hundred and sixty patients were enrolled. Of these, 485 patients (154 in the placebo group and 331 in the sumatriptan group) took the trial drug for at least 1 migraine attack and all of them were included in the safety analysis. The primary analysis was predefined as ITT analysis. Four hundred and eighty five patients with the 1st attack, 411 patients (131 in the placebo group and 280 in the sumatriptan group) with the 2nd attack and 362 patients (111 in the placebo group and 251 in the sumatriptan group) with the 3rd attack were included the ITT analysis. PP analysis of the 1st attack included 375 patients (116 in the placebo group and 259 in the sumatriptan group), excluding 110 patients from the ITT analysis. The most common reason for excluding those patients was "took an additional drug earlier than the protocol permitted".

The primary endpoint, the response rate as a percentage of patients with headache response 4 hours after administration at the first attack was 32% (44/137) in the placebo group and 62% (178/285) in the sumatriptan group. The response rate in the sumatriptan group was significantly higher than in the placebo group (Mantel-Haenszel χ^2 test; $p<0.001$). The response rates at the 2nd attack were 38% (43/113) in the placebo group and 59% (148/251) in the sumatriptan group, and the rates at the 3rd attack were 42% (40/95) in the placebo group and 59% (128/216) in the sumatriptan group. The

response rates for both attacks in the sumatriptan group were significantly higher than the placebo groups (Mantel-Haenszel χ^2 test; the 2nd dose: $p<0.001$, the 3rd dose: $p=0.005$).

The secondary endpoint, the response rate as a percentage of patients with headache response at 0.5, 1, 2 and 3 hours after administration, in the sumatriptan group was significantly higher than placebo group at any time-point apart from 1 hour after administration (Mantel-Haenszel χ^2 test; 0.5 hours after: $p<0.05$, 2, 3, 4 hours after: $p<0.001$). The percentage of patients with no pain after administration of the trial drug was 4% (6/140) in the placebo group and 22% (65/293) in the sumatriptan group at 2 hours after administration, and 15% (20/137) in the placebo group and 43% (122/285) in the sumatriptan group at 4 hours after administration. At any time-point, the percentage of patients with no pain in the sumatriptan group was significantly higher than in the placebo group (Mantel-Haenszel χ^2 test: $p<0.001$ for all). The percentage of patients with Grade 0 clinical disability (able to function as normal) was higher in the sumatriptan group than in the placebo group at, and beyond, 2 hours of administration. The percentage of patients without nausea and photo/phono-phobia was also higher in the sumatriptan group than in the placebo group at, and beyond, 2 hours of administration.

With regard to headache response for recurrent headache, the percentage of patients who experienced recurrence of headache between 4 and 24 hours after the first treatment, among patients who responded to the treatment of the first attack at 4 hours after the treatment, was similar, 41% (18/44) in the placebo group and 36% (64/178) in the sumatriptan group. The response rates at 4 hours after dosing in patients who took placebo for the 1st attack then took placebo (6 patients) or 50mg sumatriptan (12 patients) for recurrent headache were 60% (3/5) and 75% (9/12), respectively. The response rates at 4 hours after dosing in patients who took 50mg sumatriptan for the 1st attack then took placebo (29 out of 57 patients) or 50mg sumatriptan (28 out of 57 patients) for recurrent headache were 43% (12/28) and 73% (19/26), respectively, suggesting a higher response rate for recurrent headache in patients who took 50mg sumatriptan for the recurrent headache compared with patients who took placebo.

With regard to adverse events with the initial treatment, the incidence of adverse events after administration of the trial drug for all or any of the 1st to the 3rd migraine was 20.5% (32/156) in the placebo group and 24.7% (82/332) in the 50mg sumatriptan group. The incidence of severe adverse events was 5.1% (8/156) in the placebo group and 4.2% (14/332) in the 50mg group. The common adverse events (2% or more) were "nausea and vomiting NOS" in the placebo group and "parathesia NEC", "floating dizziness (excluding spinning vertigo)", "nausea and vomiting NOS" and "malaise and fatigue" in the sumatriptan group. The incidence of adverse events relevant to the trial drug (adverse drug reaction) was 7.7% (12/156) in the placebo group and 14.8% (49/332) in the sumatriptan group.

The incidence of adverse events in the treatment of recurrence was 10.5% (4/38) in the placebo + placebo group, 16.7% (7/42) in the placebo + sumatriptan group, 8.0% (8/100) in the sumatriptan + placebo group and 15.7% (14/89) in the sumatriptan + sumatriptan group. In the sumatriptan + sumatriptan group, "eating disorder NEC" was reported more than once as an adverse event relevant to the trial drug (adverse drug reaction). Serious adverse events were observed in three patients (sigmoid tumour, pregnancy (abortion) and breast cancer; 1 event per patient), though the investigators assessed they were not relevant to the trial drug. Twelve patients were withdrawn from the study due to the adverse events. These events seen in the sumatriptan group that were relevant to the trial drug were chest tightness (severe, clearly relevant) in 1 patient, nausea and vomiting NOS (severe, may be relevant) in 1 patient, malaise and fatigue (moderate, clearly relevant) in 1 patient, blindness NEC, decreased vision, hypesthesia and sweating (severe, probably relevant) in 1 patient, nausea and vomiting NOS (moderate, may be relevant), floating dizziness (excluding spinning vertigo), malaise and fatigue (moderate, clearly relevant), musculoskeltal pain, paraethesia NEC, signs and symptoms in throat and tonsils (severe, clearly relevant) in 1 patient.

G-2 Summary of Evaluation by the Evaluation Centre

(1) Efficacy

The Japanese dose-response study (GW102-201) was used as a bridging study of the study S2CM09 and overseas study results were extrapolated. As responses seen in the

placebo group in Japan were about 10% better than abroad, the Evaluation Centre requested explanations on possible differences in migraine patients who may use sumatriptan in Japan and the West. The applicant presented following arguments based on the epidemiology in Japan and the West. (i) The prevalence of migraine in Japan and the West was similar and was higher in female than male. The male and female ratio was also similar. (ii) Looking at the types of migraine, the proportions of male patients with migraine without aura and with aura were similar, but in female, the proportion of patients with "migraine without aura" was higher. (iii) The rate of migraine patients with family history was similar. (iv) The proportion of migraine patients with concurrent tension headache was almost the same. The applicant also suggested that the most likely factor which caused the 10% difference (Japanese>West) in headache response 4 hours after administration in the placebo groups in the Japanese and Western studies was the proportion of patients with concurrent tension headache in the study GW102-201 (see below for the rate of patients with concurrent tension headache). The Evaluation Centre also requested explanation on the differences in diagnosis and clinical environment of the treatment in Japan and the West. The applicant replied that "Migraine Classification and Diagnosis Criteria by International Headache Society" were used as classification and diagnosis criteria of headache in Japan and the West and the treatment of migraine attack and prophylactic treatment of migraine were similar apart from use of triptans. They also referred to the current status of treatment, suggesting that the preparation of the treatment environment of migraine was more advanced in the West, as so-called headache clinics, which specialised in examination of headache, were more common in the West than in Japan and few Japanese patients with migraine visit medical facilities. The Evaluation Centre accepted the above responses.

With regard to the complete clinical data package, the Evaluation Centre asked the applicant to clarify the reasons for not including particular data in this submission. The applicant supplied the following reasons for each study not included in the submission.

a. This was an early dose selection study that took place before 50mg was chosen as the recommended dose in the West.
b. This was a study investigating efficacy and safety of doses higher than the recommended dose at the time, 100mg.

c. The primary endpoint of the efficacy was assessed at a time other than 4 hours after administration.
d. The study investigated combination therapy with other agents (including different routes of administration)
e. This was a comparison study with drugs (dosage forms) not used in Japan.
f. The study used a different primary endpoint from headache response (a reduction from severe (Grade 3) or moderate pain (Grade 2) to mild (Grade 1) or no pain (Grade 0)).
g. The study was implemented abroad by a company other than GalxoWellcome and no details were available.
h. The targeted patients or the selection criteria of patients were different.
i. The study was a pilot study.
j. The dosage form of the drug was not the same.

In order to investigate safety data in full, the Evaluation Centre requested the applicant to include safety data from the studies that were not chosen because they were not suitable for assessment of efficacy, wherever possible. The applicant presented a summary of adverse events seen in patients (7948 in total), including events seen in placebo control studies implemented in the West (S2B206, S2B216, S2CM07, S2CM09).

The Evaluation Centre accepted the above responses.

The plasma concentration profile of an oral dose of sumatriptan was bimodal and shows the first peak within 1.5 hours of administration. In clinical studies abroad, both the 50 and 100mg groups showed significantly better headache response after 2 hours from the administration than in the placebo group. However, in the Japanese study, a significant effect was not seen 2 hours after administration compared with placebo. The Evaluation Centre requested an explanation of this. The applicant replied that, when looking at chronological changes in severity of headache at Hour 0 and Hour 2, reductions in the percentages of patients who had severe pain (Grade 3) in the sumatriptan groups (the 50mg group: 47 ? 14%, the 100mg group: 43% ? 12%) were greater than in the placebo

group (47% ? 23%). At the same time, the percentage of patients who had no pain was higher than the placebo group (the placebo group: 17%, the 50mg group: 25% and the 100mg group: 21%). The applicant argued that when comparing distribution of severity of headache at 2 hours after administration with the placebo group, the sumatriptan groups showed better improvement, although it was not reflected to headache response because "response" was defined in this study as a reduction of severe (Grade 3) or moderate (Grade 2) pain to mild (Grade 1) or no pain (Grade 0). The Evaluation Centre accepted the argument.

The primary endpoint was assessed at 4 hours after administration, but some patients may have had no pain from a natural cause by then. The Evaluation Centre asked the applicant's view on whether the efficacy of sumatriptan was fully demonstrated with headache response 4 hours after administration, which was chosen as primary endpoint. The applicant responded that when they were implementing clinical studies in Europe (S2CM07, S2CM09) from (year) till (year), they decided to use the response rate 4 hours after administration as the primary endpoint based on their judgement that response rate 4 hours after administration was more appropriate than the response rate 2 hours after administration in demonstrating chronological clinical effect of sumatriptan. They also stated that the same assessment methods as the study S2CM09 was used in the Japanese clinical study (Study GW102-201), because this study was positioned to investigate the similarities in the overseas dose-response study (Study S2CM09) and to assess a possibility of extrapolation of the overseas phase III study (Study S2CM07) to the Japanese population.

In the Japanese clinical study, the response rate in the placebo group was higher. The Evaluation Centre asked the applicant to present a result of stratified analysis, because many patients in Japan were expected to be classified as a mixed type having both migraine and tension headache. In addition, the Evaluation Centre questioned if the applicant considered the pathology of migraine in Japan and the West to be the same and if they expected a similar headache response to the West. The applicant indicated that the percentage of patients with concurrent tension headache in patients who were enrolled in the Japanese dose-response study was 35% (27/78) in the placebo group,

34% (26/76) in the 50mg group and 38% (28/74) in the 100mg group, whereas only 3 patients out of 653 patients in the placebo, 50 and 100mg groups of the study S2CM09 had concurrent tension headache. They also stated that the response rate in a group of patients with concurrent tension headache in the placebo group of the Japanese dose-response study (FAS) was 55.6%, showing a higher response rate than the response rate (43.1%) in a group of patients without concurrent tension headache. They concluded that one of the reasons for the higher response rate in the placebo group in this study was that about 1/3 of enrolled patients had concurrent tension headache. Epidemiologically, the percentage of migraine patients with concurrent tension headache was 50% in Canada (Can J Neurol Sci 20: 131-137, 1993), and according to two surveys, it was 83% (Arch Neurol 49: 914-918, 1992) and 80% (Pain 67: 501-506, 1993) in Denmark. In Japan, 43.6% of migraine patients had other types of headache concurrently, including tension headache. The applicant, therefore, considered that there was no pathological difference in migraine in the Japanese and Western populations, and concluded that the treatment effect of sumatriptan on migraine was the same as in the West. The Evaluation Centre accepted the above responses.

(2) Safety

Throughout Japanese and Western clinical studies, about 3% of patients in the 50 or 100mg groups showed chest pain and chest pressure, and also vasospastic angina (variant angina) is considered to be more common in Japan then in the West ("Ischemic Heart Disease Treatment Guideline" J Japan Medial Ass (Suppl) 109 (12):9, 1993, J Clini Experimental Medicine 192: 60-63, 2000). The Evaluation Centre asked the applicant to investigate the possibility of sumatriptan inducing ischemic coronary diseases through spasm when sumatriptan was used in Japan. The applicant suggested that although there was no epidemiological survey comparing this in Japan, it was believed that variant angina due to coronary artery spasm was more common in Japan than in the West. In addition, it was reported that a stronger constriction with spasm inducers (ergonovine or acetylcholine) was observed even in non-spastic coronary artery and the coronary artery was tenser than in Westerners (Cardiologist 4(7): 515-516, 1999). They also stated that the detailed mechanism of coronary artery spasm was largely unknown, although involvements of factors and pathologies, such as diurnal variations, automatic

nerves, vascular endothelium, NO, oxidative stress, magnesium, smoking and eNOS gene mutations, were suggested, and they speculated that all those factors would be involved in a complex way. Additionally, the applicant presented a report made by Nilsson et al. (Eur J Pharmacol 372: 49-56, 1999) showing an expression of 5-HT_{1B} receptor in the smooth muscles of the human isolated coronary artery. They argued that although 5-$HT_{1B/1D}$ receptor agonists including sumatriptan showed a vasoconstriction action on the human isolated coronary artery, the vasoconstriction with sumatriptan was far weaker than constriction of the brain blood vessels, as it was with other triptans. As no epidemiological survey of the incidence of variant angina in Japanese and Western populations was available, it was not possible to discuss the difference in the incidence of variant angina with use of sumatriptan. The applicant stated, however, as variant angina from coronary artery spasm was more common in Japan, ethnic differences in the pathology and vasoreactivity were reported, the detailed mechanism was mostly unknown and sumatriptan, as well as other 5-$HT_{1B/1D}$ receptor agonists, had a potential to cause coronary artery spasm; the applicant decided to "contraindicate" use of sumatriptan in patients with or with a sign of ischemic heart diseases including variant angina, and to "administer carefully" to patients with a potential of ischemic heart disease, in order to assure safety in patients with ischemic heart diseases including variant angina.

In literature, it was suggested that sumatriptan had a stronger constriction action on the coronary artery than other triptans (Neurology 55: 1524-1530, 2000). The Evaluation Centre instructed the applicant to analyse relevancy of sumatriptan on the patients who developed ischemic heart diseases in clinical studies and to investigate the possibility that chest pain in the patients was caused by coronary artery ischemia. Furthermore, the Evaluation Centre requested a comparison of the incidences of angina and myocardial infarction in post-marketing reports with other triptans. The applicant showed that no angina was observed in Japan (Study GW102-201), angina was observed in 1 patient in the 100+100mg group and 1 patient in the 100mg + placebo group (both developed within 24 hours of the initial administration) in the study S2CM09 abroad, which was moderate in both patients and ameliorated, 1 of them had concurrent hypercholesteremia, the investigators ruled out involvement of sumatriptan in both cases and they were not

specified as vasospastic angina, and no angina was observed in the study S2CM07. With regard to chest symptoms, they showed that 1 patient in the 50mg group and 3 patients in the 100mg group of the Japanese study GW102-201 reported "chest pain NEC", but all were mild and transient, 1 of the 3 patients in the 100mg group (developed on Day 4, not relevant) had concurrent hyperlipidemia and diabetes, and in the overseas clinical studies, the incidence of chest symptoms in the study S2CM09 and the study S2CM07 were similar, around 3%, and most of them were transient. With regard to the cause of chest symptoms, Houghton LA et al (Lancet 344: 985-986, 1994) and Forster JM et al. (Aliment Pharmacol Ther 13: 927-936, 1999) reported that cases without ECG changes after administration of sumatriptan (injection) showed significant increases in the strength of the oesophagus constrictions and duration of constriction, and, at the same time, they experienced chest pain, thus suggesting chest symptoms which were believed to be caused by the heart may be caused by an effect on the oesophagus function. In addition, there were reports that no ECG change was observed when chest symptoms were developed after administration of sumatriptan (injection). Therefore, the applicant suggested, all of the chest symptoms observed after administration of sumatriptan were not necessarily caused by coronary artery diseases. With regard to the post-marketing reports, according to the latest xxxx aboard (October 1999 to March 2000), x events (x patients) of myocardial ischemia were reported as serious and known adverse events in the 6 months. Their breakdown was x events of myocardial infarction, x events of subendocardial infarction, x events of heart arrest, x events of coronary artery spasm and x events of angina. Considering that x patients out of these x patients had risk factors of cardiovascular disorders and the number of prescribed sumatriptan in this period was x, the applicant argued, the incidence of adverse drugs reactions relating to myocardial ischemia was low, providing patients with risk factors were excluded. With regard to comparison of incidences of ischemic heart diseases observed with other triptans, the applicant suggested that according to overseas prescribing information, the incidences of angina and arrhythmia with any triptans were low, less than 0.1% and less than 1%, respectively, and the incidences of adverse events with chest symptoms were similar and all between 2 and 4 %, therefore, the incidences of ischemic heart diseases with sumatriptan and other triptans were low and similar.

The Evaluation Centre asked the applicant if there were reports of ischemic heart disease following use of already approved sumatriptan injection in Japan. The applicant replied that from the launch, x products were shipped out, although the actual volume of prescription was unknown, and x adverse drug reactions relating to chest symptoms (chest pressure, anginal syndrome, distressed feeling of chest, etc.,) were observed in x patients and of those, x events in x patients were serious, x events in x patients were moderate and the rest were mild. Of those x events, x events, including x serious events, had examinations including ECG monitoring during the events. None of ECGs showed abnormality and there was no patient who was confirmed to have had ischemic heart disease such as angina and myocardial infarction because of sumatriptan (injection). Furthermore, the applicant presented a report by a group from the neurology department of the Kitazato University given in the Headache Research Seminar of the 5th Congress of the European Federation of Neurological Societies (Denmark) in October 2000. According to the report, 3mg of subcutaneous sumatriptan was administered to 41 patients with 56 migraine attacks and their ECG was monitored before and up to 5 minutes after the administration. Chest symptoms (chest discomfort, chest pressure) were found in 5 patients (8 events) and, of these, 3 patients (5 events) had ECG monitoring for 5 minutes after administration. No ischemic changes in the coronary artery were found. The Evaluation Centre accepted those responses.

As sumatriptan injections are already on the market, there is a possibility that the injection is administered just after the tablet was taken or, conversely, the tablet is taken just after the injection was administered because of recurrence or a poor effect. The Evaluation Centre questioned the applicant if there was a need to include a caution in the prescribing information (draft). The applicant explained that although such a situation was possible, as no clinical study investigating a combination of an injection and a tablet was conducted, they were unable to specify acceptable interval of administration with any supporting data, and the prescribing information in the UK and the USA did not specify an acceptable administration interval of the injection and the tablet. The applicant responded, therefore they were going to add in the Precaution for Use Relating to Dosage and Administration (Draft): “When administering Imigran Tables 50 to treat recurrence of an attack after the initial treatment with sumatriptan succinate injection

(Imigran Injection 3), or vice versa, pay full attention, as there is little clinical experience." The Evaluation Centre considers these responses acceptable, but would like to refer to the expert review.

(3) Dosage and Administration Method

With regard to the rationales of the Dosage and Administration Method, the Evaluation Centre requested an explanation for allowing the dose to be increased to up to 100mg/dose, because the response rate of the primary endpoint, headache response 4 hours after administration, was higher in the 50mg group than the 100mg group and some secondary endpoints also showed better results in the 50mg group than in the 100mg group. The applicant presented the following rationales of allowing the dose to be increased to up to 100mg. 1) The dose-reaction study in Japan (GW102-201): (i) When looking at chronological changes, the response rate at 2 hours after administration was higher in the 100mg group (54.4%) than in the 50mg group (42.0%). (ii) When looking at chronological changes in the response rate of patients with severe (Grade 3) pain at administration, the response rate at 2 hours after administration was higher in the 100mg group (55.2%) than in the 50mg group (28.1%). (iii) When looking at chronological changes in the percentage of patients with no pain, the percentage at 3 hours after administration was also higher in the 100mg group (40.0%) than in the 50 mg group (25.0%). 2) The dose-response study abroad (S2CM09): (i) When looking at chronological changes in the percentage of patients with no pain, the percentage at 3 hours after administration was higher in the 100mg group (52%) than in 50mg group (43%). (ii) When looking at chronological changes in patients with severe (Grade 3) pain at administration, the percentage of patients with no pain at 3 hours after administration was higher in the 100mg group (46.7%) than in the 50mg group (33.3%). Based on 4 clinical studies that confirmed efficacy of 100mg or lower dose of sumatriptan abroad (S2CM09, S2CM07, S2CM10, S2CM11), the applicant indicated that more patients chose 50 or 100mg than 25mg when they were asked to choose the dose level based on the overall impression of the patients in the study S2CM11, the percentage of patients with no pain in the study S2CM11, which was the secondary endpoint, was significantly higher in the 100mg group than in the 50mg group at 3 and 4 hours after administration and some patients who were given 50mg in the study S2CM10 were not satisfied and

chose to take 100mg. As above, the applicant pointed out that, when early onset of response was required in patients with, for example, severe pain, 100mg provided an option, which would provide faster response; even though each patient would show a different degree of satisfaction on headache relief, some patients actually considered treatment with 100mg was appropriate when they were asked to select the dose based on their impression; and types and severity of adverse drug reactions in the 50 and 100mg groups were similar in all studies. The applicant concluded that that was the reasons for setting the dosage as "the dose may be increased to up to 100mg/dose". The Evaluation Centre accepted the above responses.

Including an additional dose at a recurrent attack, the maximum dose will be 200mg/day. There was no data on taking 100mg twice in a short time in a Japanese study in migraine patients. Therefore, the Evaluation Centre requested the applicant to explain if they can assure the safety. The applicant stated that in the study S2CS01 in Europe, the efficacy and safety of sumatriptan was investigated by administering 100mg of sumatriptan to migraine patients during an attack then all patients received additional 100mg or the placebo 2 hours after the initial administration. In total, 1,246 patients received 100mg of sumatriptan for at least 1 attack (Attack 1) and then took additional sumatriptan or placebo 2 hours later. The incidences of adverse events were 34% (148/432) in the 100mg+100mg group and 33% (140/420) in the 100mg + placebo group. The incidence of severe adverse events were 7% (31/432) in the 100mg + 100mg group and 9% (38/420) in the 100mg + placebo group. The study did not show a higher incidence of adverse events with an additional dose of sumatriptan or worsening of severity of adverse events, and also there was no difference in the incidence of adverse drug reactions in the two groups. Although there was no difference in the incidence of cardiovascular disorders and chest adverse events, 4.2% (18/432) in the 100mg + 100mg group and 4.5% (19/420) in the 100mg + placebo group, 6 patients in the 100mg + 100mg group and 3 patients in the 100mg + placebo group showed severe adverse drug reactions. Their breakdown was; 2 cases of tachycardia, 1 case of head throbbing, 1 case of tightness of chest and 1 case of chest pressure in the 100mg + 100mg group; and 1 case of hot flush, 1 case of hypotension, 1 case of pallor and 1 case of chest pain in the 100mg + placebo group. Furthermore, 1 patient in the 100mg + 100mg groups showed

myocardial infarction and the investigator assessed it was “unlikely to be relevant” to the trial drug and the applicant stated the condition was improved after completion of the study. In response, the Evaluation Centre requested the applicant to explain a possible increase in serious cardiovascular adverse drug reaction when 100mg was administered twice in a short interval, as slightly more severe cardiovascular adverse drug reactions were observed in the 100mg + 100mg group and 1 event of myocardial infarction was observed. The applicant presented a list of severe cardiovascular adverse events observed in the study S2CS01 and explained that the most of the events occurred on the initial administration and relevancy of an event to the additional administration of 100mg was positive only in 1 patient. The applicant also stated that myocardial infarction seen in 1 patient was developed 1.5 months after administration of the trial drug and they believed it was unlikely to be related to the trial drug. They also showed that, according to the data, which the list of adverse events in the US label was based on (2,609 cases in 100mg group, 830 cases in the 100mg + 100mg group), the incidence of cardiovascular adverse events was 2.06% in the 100mg group and 1.68% in the 100mg + 100mg group and the incidence of chest symptom adverse events was 1.76% in the 100mg group and 2.04% in the 100mg + 100mg group. As above, there is no clear tendency of an increase in cardiovascular adverse events with administration of 100mg + 100mg, however, the Evaluation Centre would like to assess appropriateness of an additional dose of 100mg considering discussion during the Expert Review.

3. Result from a Compatibility Check by OPSR and Interpretation by the Evaluation Centre

(1) Interpretation of the Compatibility Check

The OPSR has carried out an audit on documents as stipulated in the last paragraph of Section 4, Article 14 of the Pharmaceutical Affairs Law. There was incompatibility in some parts (e.g. protocol violations in some clinical study results). However, the

Evaluation Centre considered that there was no problem in carrying out the evaluation based on the approval evaluation data submitted.

(2) Interpretation of the GCP Inspection

In the GCP meeting, the submission was considered to be GCP compliant. The Evaluation Centre considered that there was no problem in carrying out the evaluation based on the approval evaluation data submitted.

4. Overall Assessment of the Evaluation Centre

As a result of the evaluation described above, the Evaluation Centre concluded that Imigran 50 was approvable. However, the Evaluation Centre believes that the Dosage and Administration Method, especially regarding propriety of the additional dose of 100mg, needs to be discussed further in the Expert Review.

Evaluation Report (2)

27th April, 2000

[Product Name]: Imigrain Tablet 50
[Non-proprietary Name]: Sumatriptan succinate
[Applicant]: Glaxo SmithKline KK
(at the filing, it was GlaxoWellcome KK)
[Submission Date]: 2nd August 2000 (a manufacturing approval application)

1. Evaluation Detail

Based on the Evaluation Report (1), the Evaluation Centre asked opinions of experts in the committee. This is to report the outcome of the evaluation based on the discussion with the committee members.

E. Pharmacology

The Expert Committee indicated that appropriateness of the models used in the pharmacology studies should be explained, although the mechanism of migraine attack was unknown. The applicant submitted a summary of the latest information on distributions of 5-HT receptors in human cerebral blood vessels, information processing in cells and mechanisms of vasoconstrictions. The Evaluation Centre considered these were appropriate, in view of the current scientific standards. The Expert Committee advanced their opinion that the superiority of sumatriptan against ergotamine was not shown in the submitted data. The applicant indicated that sumatriptan and ergotamine had different selectivity on various receptors and ergotamine possessed a stronger constriction action on the coronary artery compared with sumatriptan. The Evaluation Centre accepted the responses.

F. Absorption, Distribution, Metabolism and Excretion

The applicant had explained that low BA of an oral dose was a consequence of the first pass effect based on high absolute BA of a subcutaneous dose. Based on discussions in the expert review meeting, the Evaluation Centre asked the applicant to provide pharmacokinetic parameters, absorption rates, etc., of an intravenous dose and explain it

again. The responses of the applicant were as follow. The absolute BA of a subcutaneous dose was 96% and the BA of an oral dose relative to a subcutaneous dose was 14.3%, therefore, BA of Imigran Tablets was considered to be approximately 14%. When healthy adult males received an oral dose of radiolabelled sumatriptan, approximately 60% and 40% of radioactivity was collected from the urine and faeces, respectively, therefore, the absorption rate was considered to be approximately 60%. Furthermore, as approximately 3% of the dosed amount was excreted to the urine as unchanged sumatriptan, suggesting that metabolism such as the first pass effect, etc., influenced BA and made it low. The Evaluation Centre accepted these responses, i.e., the reasons for low BA were due to up to around 40% of sumatriptan being unabsorbed and the first pass effect after absorption through the digestive tract.

Based on the Dosage and Administration Method of Imigran Tablets, if headache recurred as short as 2 hours after the first administration, the patients are allowed to take an additional dose, however, on the other hand, based on the average blood concentration profile, the blood concentration remains high at 2 hours after administration. Therefore, the Evaluation Centre asked the applicant to discuss the reason for recurrence of migraine. The applicant replied that, although detailed mechanisms were unclear, blood concentration profiles in patients showed individual differences and patients with fast absorption reached C_{max} early and then the blood level started to fall, therefore, as a result, migraine attacks may be seen in a short period of time. The efficacy of Imigran Tablets for a recurrent headache was confirmed in the study S2CM09, which demonstrated a high response rate of the sumatriptan groups compared with the placebo group. Also, an additional administration of 100mg sumatriptan at the minimum of 2 hours after administration of 100mg was believed not to present safety issues. Therefore, the applicant concluded, the administration interval was set as the same as abroad, i.e., 2 hours or more. The Evaluation Centre accepted those responses.

G. Results of Clinical Studies

1) Efficacy

Based on a discussion during the expert review, the efficacy evaluation of Imigran Tablets was thought to be appropriate.

With regard to the Dosage and Administration Method, 50mg was used as the first dose and 25mg was not investigated. Some experts expressed their opinion that some effect may be seen with 25mg. The applicant presented the following responses. In the dose-response study abroad (Study S2CM09, xxxx), "the response rate 4 hour after administration" in the groups receiving 25, 50 and 100mg sumatriptan was significantly superior to the placebo group, but the response rate in the 50 and 100mg groups was statistically significantly superior to the 25mg group. The incidences of adverse drug reactions in the 25 and 50mg groups did not show a large difference. Therefore, the applicant believed that there was no need to investigate efficacy of 25mg in Japan as the efficacy of 50mg was higher than 25mg and the incidences of adverse drug reactions did not show a large difference. The Evaluation Centre accepted the reply.

2) Safety

Although the maximum dose in 24 hours was 200mg, no study in Japanese patients receiving 200mg was conducted, so the expert committee members questioned the safety in Japanese. The applicant made the following points. (1) Pharmacokinetics of sumatriptan in the Japanese and overseas populations were similar. (2) In the pharmacokinetic study program in overseas healthy adult volunteers, a single oral dose study of doses up to 400mg was conducted and good tolerability was seen. (3) The plasma concentration profiles were simulated based on the plasma concentration profile when a single oral dose of 100mg sumatriptan was administered to Japanese healthy volunteers. Based on the simulation, the plasma concentration after an additional dose of 100mg, which was administered 2 hours after a single dose of 100mg, was expected to be lower than when a single dose of 200mg was administered. (4) In the overseas clinical studies, the types and incidences of adverse events/adverse drug reactions, and the incidences and severity of cardiovascular adverse drug reactions and adverse drug reactions with chest symptoms seen when an additional 100mg was dosed 2 hours after the initial 100mg dose were not largely different from when 100mg was administered.

(5) When safety in clinical studies carried out in Japan and abroad was compared, the types, incidences, severity, etc., of adverse drug reactions observed did not have a large difference. Based on these, the applicant believed that administration of 100mg twice with a 2-hour or longer interval in Japanese migraine patients did not present new safety issues, as it did not in the Western population. They also added that the safety data of 200mg sumatriptan within 24 hours in Japanese patients were going to be collected in the post-marketing surveillance and, if there were some issues, they would review a need to conduct a special investigation. The Evaluation Centre accepted those responses.

The Expert expressed an opinion that migraine patients with unbearable pain may overdose expecting a better effect. The applicant replied that no data from acute toxicity studies (rats and dogs) and general pharmacology studies suggested dependency to sumatriptan. They also added that they were going to provide information actively, including giving advice on how to take the drug correctly to patients, so that the drug was used correctly and to avoid overdose. The Evaluation Centre accepted these responses.

As sumatriptan was a 5-HT receptor agonist, a potential of sumatriptan to initiate serotonin syndrome was questioned. The applicant replied that involvements of 5-HT_{1A} and 5-HT_2 receptors in serotonin syndrome were suggested and seretonin syndrome was known to be developed when monoamine oxidase inhibitors and selective serotonin reuptake inhibitors (SSRI) were taken singularly or concomitantly. As sumatriptan selectively affected 5-$HT_{1B/1D}$, the applicant believed that monotherapy with sumatriptan was unlikely to cause serotonin syndrome. The applicant stated that, so far, 3 patients were reported to have developed serotonin syndrome after administration of sumatriptan injection. Two of these used SSRI concomitantly and the remaining 1 patient developed the syndrome more than 24 hours after sumatriptan administration. Therefore, they believed that the relevancy to sumatriptan was low. The Evaluation Centre accepted the above responses.

To make sure the drug is used appropriately and safely, the following changes in the prescribing information were made. (i) As efficacy of use other than administration

during migraine attacks, for example prophylactic use, was not proven, the cautions were amended to include this point. (ii) A statement instructing to repeat tests, etc., when a patient was not responding to sumatriptan treatment, so that diseases other than migraine were not missed through needless treatment with sumatriptan. (iii) As sumatriptan injections have been commercially available, a caution on concomitant or additional use of injections was added. (iv) As individual differences in pharmacokinetic of sumatriptan are large, information on this point was added to the pharmacokinetic section.

3) Miscellaneous

The outline of a post-marketing surveillance plan was submitted. The Evaluation Centre confirmed that the plan contained investigations of the use of an additional dose within 24 hours and the efficacy and safety in these cases, and safety of the daily maximum dose (200mg).

2. Overall Assessment

Based on the above evaluation, the Evaluation Centre concluded that there was no problem in approving this drug, based on the submitted application data.

As this is a drug with a new administration route, the re-examination period should be 6 years. The Evaluation Centre decided to dedicate the drug product as a “powerful drug”.

18th May 2001
Evaluation and Licensing Division,
Pharmaceutical and Medical Safety Bureau

Evaluation Report (2)

Product Name:	Imigrain Tablet 50
Non-proprietary Name:	Sumatriptan succinate
Applicant:	Glaxo SmithKline KK
	(at the filing, it was GlaxoWellcome KK)
Submission Date:	2nd August 2000 (a manufacturing approval application)

[Evaluation Outcome]

There is no problem in approving this drug, providing the shelf life is amended to "2 years".

(Remarks)

The applicant submitted additional study results on stability. The PMDEC has evaluated them and assessed it was appropriate to extend the shelf life of the product to 2 years.

1st June, 2001
Evaluation and Licensing Division,
Pharmaceutical and Medical Safety Bureau

Evaluation Report (3)

Product Name:	Imigrain Tablet 50
Non-proprietary Name:	Sumatriptan succinate
Applicant:	Glaxo SmithKline KK
	(at the filing, it was GlaxoWellcome KK)
Submission Date:	2nd August 2000 (a manufacturing approval application)

[Evaluation Outcome]

Based on the view in the 1st Committee on Drug Meeting (held on 18th May 2001), the Dosage and Administration Method of Imigran Tablet 50 should be changed as follows.

<Before>

Usually in adults, when experiencing a migraine headache, 50mg/dose of sumatriptan should be taken orally.

Depending on the condition, the dose may be increased to 100mg/dose. An additional dose of sumatriptan may be taken for a recurrence of migraine after successful treatment or if the initial treatment is not satisfactory. However, the additional dose should be at least two hours after the initial treatment and the total daily dose should not exceed 200mg.

<After Change>

Usually in adults, 50mg/dose of sumatriptan should be taken orally when experiencing a migraine headache.

If the effect is not satisfactory, an additional dose may be taken, but there should be an interval of more than 2 hours from the initial dose.

If an oral dose of 50mg did not provide a satisfactory effect, the patient may take an oral dose of 100mg for the next migraine attack.

However, the total daily dose should not exceed 200mg.

This amendment does not alter the outcome of the evaluation.