Health Canada Santé Canada

SUMMARY BASIS OF DECISION (SBD)

^{Pr}PRADAX™

Dabigatran etexilate, 75 mg and 110 mg capsules

Boehringer Ingelheim Canada Ltd.

Submission Control No. 114887

Date Issued	2008/11/06

Health Products and Food Branch

Canada

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- promoting conditions that enable Canadians to make healthy choices and providing information so that they can make informed decisions about their health.

Health Products and Food Branch

Également disponible en français sous le titre : Sommaire des motifs de décision (SMD), ^{Pr}PRADAX^{MC}, Dabigatran etexilate, gélule, 75 mg et 110 mg, Boehringer Ingelheim (Canada) Ltée, N^{o} de contrôle de la présentation 114887

FOREWORD

Health Canada's Summary Basis of Decision (SBD) documents outline the scientific and regulatory considerations that factor into Health Canada regulatory decisions related to drugs and medical devices. SBDs are written in technical language for stakeholders interested in product-specific Health Canada decisions, and are a direct reflection of observations detailed within the evaluation reports. As such, SBDs are intended to complement and not duplicate information provided within the Product Monograph.

Readers are encouraged to consult the 'Reader's Guide to the Summary Basis of Decision - Drugs' to assist with interpretation of terms and acronyms referred to herein. In addition, a brief overview of the drug submission review process is provided in the Fact Sheet entitled 'How Drugs are Reviewed in Canada'. This Fact Sheet describes the factors considered by Health Canada during the review and authorization process of a drug submission. Readers should also consult the 'Summary Basis of Decision Initiative - Frequently Asked Questions' document. These documents are all available on the Health Canada website.

The SBD reflects the information available to Health Canada regulators at the time a decision has been rendered. Subsequent submissions reviewed for additional uses will not be captured under Phase I of the SBD implementation strategy. For up-to-date information on a particular product, readers should refer to the most recent Product Monograph for a product. For information related to post-market warnings or advisories as a result of adverse events, interested parties are advised to access the Health Canada website.

For further information on a particular product, readers may also access websites of other regulatory jurisdictions, available under 'Related Links' on the Health Canada website. The information received in support of a Canadian drug submission may not be identical to that received by other jurisdictions.

Other Drug Policies and Guidance:

Readers should consult the Health Canada website for other drug policies and guidance documents. In particular, readers may wish to refer to the 'Management of Drug Submissions Guidance'.

TABLE OF CONTENTS

1 PRODUCT AND SUBMISSION INFORMATION

Brand Name	PrPRADAX™
Manufacturer/Sponsor	Boehringer Ingelheim Canada Ltd.
Medicinal Ingredient	dabigatran etexilate, as dabigatran etexilate mesilate
International Non-proprietary Name	dabigatran etexilate, as dabigatran etexilate mesilate
Strengths	75 mg and 110 mg
Dosage form	Capsule
Route of Administration	Oral
DINs	02312433 – 75 mg 02312441 – 110 mg
Therapeutic Classification	Anticoagulant
Non-medicinal Ingredients	Acacia, carragenan, dimeticone, hydroxypropyl cellulose, hypromellose, indigocarmin, iron oxide black, potassium chloride, propylene glycol, shellac, sunset yellow, talc, tartaric acid, titanium dioxide
Submission Type and Control No.	New Drug Submission, Control No. 114887
Date of Submission	2007/06/19
Date of Authorization	2008/06/10

2 NOTICE OF DECISION

On June 10, 2008, Health Canada issued a Notice of Compliance to Boehringer Ingelheim Canada Ltd. for the drug product, Pradax.

Pradax contains the medicinal ingredient dabigatran etexilate used in its salt form, dabigatran etexilate mesilate. Pradax is an anticoagulant.

Pradax is indicated for the prevention of venous thromboembolic events (VTE) in patients who have undergone elective total hip replacement or total knee replacement surgery. Dabigatran etexilate is a prodrug which is converted in plasma and liver to the active drug, dabigatran. Dabigatran is a competitive, reversible, direct thrombin inhibitor. Since thrombin enables the conversion of fibrinogen into fibrin during the coagulation cascade, thrombin inhibition prevents the development of thrombus. Dabigatran inhibits free thrombin, fibrin-bound thrombin and thrombin-induced platelet aggregation.

The market authorization was based on quality, non-clinical, and clinical information submitted. The clinical trial database evaluated >8,000 patients in the three Phase III pivotal studies. Each one of the pivotal studies was designed as a non-inferiority study in which dabigatran was compared to enoxaparin. The pre-specified primary efficacy endpoint was total VTE and all-cause mortality. Pradax was found to be non-inferior to enoxaprin in total VTE and all-cause mortality. Similar results were obtained for major VTE and VTE-related mortality. The adverse reactions that were attributed to dabigatran were those of bleeding or signs of bleeding which are typical of an anticoagulant.

Pradax (75 mg and 110 mg, dabigatran etexilate) is presented as capsules. The recommended dose of Pradax is 220 mg once daily taken orally as two capsules of 110 mg in patients with intact renal function. Treatment should normally be initiated within 1-4 hours of completed surgery once hemostasis is secured. Additional dosing guidelines are available in the Product Monograph.

Pradax is contraindicated for patients with known hypersensitivity to dabigatran or dabigatran etexilate or to any ingredient in the formulation or component of the container.

Pradax is also contraindicated for patients with the following conditions:

- Severe renal impairment;
- Haemorrhagic manifestations, bleeding diathesis, or patients with spontaneous or pharmacological impairment of haemostasis;
- Lesions at risk of clinically significant bleeding, e.g. cerebral infarction (hemorrhagic or ischemic) within the last 6 months;
- Concomitant treatment with strong P-glycoprotein inhibitors, e.g. quinidine.

Pradax should be administered under the conditions stated in the Product Monograph taking into consideration the potential risks associated with the administration of this drug product. Detailed conditions for the use of Pradax are described in the Product Monograph.

Based on the Health Canada review of data on quality, safety, and effectiveness, Health Canada considers that the benefit/risk profile of Pradax is favourable for the prevention of VTE in patients who have undergone elective total hip replacement or total knee replacement surgery.

3 SCIENTIFIC AND REGULATORY BASIS FOR DECISION

3.1 Quality Basis for Decision

3.1.1 Drug Substance (Medicinal Ingredient)

General Information

The salt form of dabigatran etexilate, dabigatran etexilate mesilate, is the medicinal ingredient of Pradax, an anticoagulant indicated for the prevention of venous thromboembolic events (VTE) in patients who have undergone elective total hip replacement or total knee replacement surgery. Dabigatran etexilate is converted to the active substance dabigatran which is a competitive, reversible, direct thrombin inhibitor that prevents the formation of blood clots.

Manufacturing Process and Process Controls

The drug substance is synthetically derived.The drug substance specifications were found to be satisfactory and the impurity limits meet ICH requirements. The processing steps have been evaluated and the appropriate ranges for process parameters have been established. The manufacturing process is considered to be adequately controlled within justified limits.

Characterization

The structure of dabigatran etexilate mesilate is considered to be adequately elucidated and the representative spectra have been provided. The results are consistent with the proposed structure of dabigatran etexilate mesilate.

Impurities and degradation products arising from manufacturing and/or storage were reported and characterized. The proposed limits are considered adequately qualified (i.e. within ICH limits and/or qualified from toxicological studies) and are therefore considered acceptable.

Control of Drug Substance

The specifications are considered acceptable for the drug substance. Data from the batch analyses were reviewed and are within the proposed acceptance criteria.

The drug substance packaging is considered acceptable.

Stability

Based on the long-term and accelerated stability data submitted, the proposed retest period, shelf-life, and storage conditions for the drug substance are supported and considered to be satisfactory.

3.1.2 Drug Product

Description and Composition

Pradax (dabigatran etexilate mesilate, a salt form of dabigatran etexilate) is presented in two strengths, 75 mg and 110 mg, in hydroxypropylmethyl cellulose (HPMC) capsules.

- The 75 mg capsule contains 86.48 mg of dabigatran etexilate mesilate corresponding to 75 mg of dabigatran etexilate base. The HPMC capsule has a light blue opaque cap, and cream-colored opaque body (size 2) filled with yellowish pellets. The cap is imprinted with the Boehringer Ingelheim company symbol, and the body is imprinted with “R75”.
- The 110 mg capsule contains 126.83 mg of dabigatran etexilate mesilate corresponding to 110 mg of dabigatran etexilate base. The HPMC capsule has a light blue opaque cap, and cream-coloured opaque body (size 1) filled with yellowish pellets. The cap is imprinted with the Boehringer Ingelheim company symbol and the body is imprinted with “R110”.

The non-medicinal ingredients in the pellets are tartaric acid, acacia, hypromellose, dimeticone, talc, and hydroxypropyl cellulose. The capsule shell contains: carragenan, potassium chloride, titanium dioxide, sunset yellow, indigocarmin, hypromellose, and purified water. The printing ink contains shellac, iron oxide black, and propylene glycol.

Pradax capsules are packaged in aluminium blister strips containing ten HPMC capsules; and in white polypropylene 80 cc bottles with a multi-part plastic closure, including a desiccant of silica gel. The bottles contain 60 HPMC capsules per bottle.

All non-medicinal ingredients (excipients) found in the drug product are acceptable for use in drugs according to the *Food and Drug Regulations*. The compatibility of dabigatran etexilate mesilate with the excipients is demonstrated by the stability data presented on the proposed commercial formulation.

Pharmaceutical Development

Changes to the manufacturing process and formulation made throughout the pharmaceutical development are considered acceptable upon review.

Manufacturing Process and Process Controls

A standard process, utilising well-established manufacturing technology, is used in the production of Pradax. The method of manufacturing is considered acceptable and the process is considered adequately controlled within justified limits.

Control of Drug Product

Pradax is tested in accordance to the specification to verify that the identity, appearance, content uniformity, active ingredient content, dissolution, and levels of degradation products are within acceptance criteria. The proposed limits are considered adequately qualified (i.e. within ICH limits and/or qualified from toxicological studies). Control of the impurities and degradation products is therefore considered acceptable.

Copies of the analytical methods and, where appropriate, validation reports are considered satisfactory for all analytical procedures used for release and stability testing of Pradax.

Stability

Based on the long-term and accelerated stability data submitted, the proposed shelf-life is considered acceptable when Pradax, packaged in aluminium blister strips and in the polypropylene bottle closure system with desiccant are stored at room temperature (between 15-30°C for bottles and 15-25°C for blisters). The in-use study supports an in-use shelf-life of 30 days for capsules stored in the polypropylene bottle container system with desiccant.

The compatibility of the drug product with the container closure system was demonstrated through compendial testing and stability studies. The container closure system met all validation test acceptance criteria.

3.1.3 Facilities and Equipment

The proposed manufacturing site met GMP requirements and complies with the requirements of Division 2 of the *Food and Drug Regulations*.

3.1.4 Adventitious Agents Safety Evaluation

No material of animal or human origin is used in the production of Pradax.

3.1.5 Conclusion

The Chemistry and Manufacturing information submitted for Pradax has demonstrated that the drug substance and drug product can be consistently manufactured to meet the approved specifications. Proper development and validation studies were conducted, and adequate controls are in place for the commercial processes.

3.2 Non-clinical Basis for Decision

Pradax (dabigatran etexilate mesilate, a salt form of dabigatran etexilate) is the prodrug of dabigatran, a novel, synthetic, specific, non-peptide thrombin inhibitor. Dabigatran etexilate mesilate (BIBR 1048 MS) is devoid of any antithrombin activity *in vitro*. However, after oral administration and absorption from the gastrointestinal tract, dabigatran etexilate mesilate is converted by esterases into the active form dabigatran (BIBR 953 ZW).

In the non-clinical studies, oral dosing was done with BIBR 1048 MS while the intravenous (IV) administration used BIBR 953 ZW.

3.2.1 Pharmacodynamics

BIBR 953 ZW has been shown to be a potent and specific inhibitor of thrombin, demonstrating anti-coagulant and anti-thrombotic activity both *in vitro* and *in vivo*. BIBR 953 ZW inhibited purified human thrombin *in vitro* with an inhibitory constant of 4.5 nM. Its selectivity was apparent through the 700-fold or larger concentrations required to inhibit other serine proteases involved in coagulation.

Anticoagulant Activity

In vitro, BIBR 953 ZW potently prolonged the activated partial thromboplastin time (aPTT), ecarin clotting time (ECT), and prothrombin time (PT) in rat, rabbit, and Rhesus monkey plasma. Human platelet aggregation was not affected by BIBR 953 ZW unless thrombin was used as the stimulus to induce aggregation.

Anticoagulant activity *ex vivo* was prolonged in a dose-dependent manner in rats, Rhesus monkeys, and rabbits. Five minutes after administration of BIBR 953 ZW in rats, the aPTT was prolonged by 15- and 45-fold after an IV bolus of 1 and 3 mg/kg, respectively. Oral administration of BIBR 1048 MS in rats, in doses between 10 and 100 mg/kg, resulted in a dose-dependent elevation of the aPTT, with a 13-fold elevation over control that peaked 30 min post dosing with the highest dose. Similar effects were also seen with Rhesus monkeys after IV and oral dosing. After a single oral dose of 5 mg/kg, there was a peak 3-fold prolongation of the aPTT values 2 hours after administration, and prolonged aPTT values could still be measured 8 hrs after dosing. Similarly in rabbits, a dose-dependent effect could be measured *ex vivo* with aPTT after IV administration of BIBR 953 ZW or after oral administration of BIBR 1048 MS.

Antithrombotic Activity

The ED_{50} is the dose that is pharmacologically effective for 50% of the population exposed to the drug. BIBR 953 ZW inhibited thrombus formation with an ED_{50} of 33 µg/kg in rats, and an ED_{50} of 66 µg/kg in rabbits, after IV administration. Complete inhibition of thrombus formation occurred with the highest IV dose of 0.1 and 0.5 mg/kg in rats and rabbits, respectively. In both species, there was an approximate linear inverse correlation between reduction of clot size and increased aPTT time. Similar results were obtained after oral dosing with BIBR 1048 MS in rats and rabbits. The test results demonstrated that dabigatran is a potent antithrombotic agent with a rapid onset of action.

Bleeding Effects

Potential bleeding side-effects were evaluated in rats. IV doses of BIBR 953 ZW 5-fold higher than the dose that resulted in complete inhibition of thrombus formation induced significant bleeding. These effects also correlated well with the aPTT prolongation, suggesting that monitoring of potential overdosing is possible. The results in this non-clinical model suggest a 5-fold safety margin between maximum antithrombotic effects and bleeding onset.

Secondary Pharmacodynamics

Secondary pharmacodynamic studies investigated effects in cardiovascular, pulmonary, central nervous system (CNS), gastrointestinal, and renal systems. A comprehensive cardiovascular profiling was performed with an assessment of both *in vitro* and *in vivo* proarrhythmic risk. The data suggest that the risk for proarrhythmic events is low. Cardiovascular studies in rats and rabbits showed very little effect. The doses given were between 20- and 100-fold greater than those that elicited antithrombotic effect. Respiratory parameters were also measured parallel to cardiovascular function in rabbits. No effect was seen at IV doses up to 10 mg/kg.

There was no effect on locomotor activity in rats and effects on the gastrointestinal tract were minimal.

Renal and liver effects were tested in dogs. After IV or oral administration, there was no effect on metabolites or electrolytes in serum. After IV administration of the highest dose, 3 mg/kg, there was a slight decrease in sodium and chloride excretion and a slight elevation in potassium excretion in urine. These effects with the highest dose were significant over control but were still within normal ranges.

Safety Pharmacology

A core battery of safety studies were conducted according to Good Laboratory Practices (GLP).

CNS testing was performed in rats after a single oral administration of 30, 100 or 300 mg/kg BIBR 1048 MS. No relevant effects on general behavior and physiological state, including body temperature, were reported at the two lower doses. At the highest dose of 300 mg/kg, there was a slight decrease in body temperature 4 and 24 hours after dosing.

Effects on respiration were tested in conscious rats administered with a single oral dose of 30, 100 or 300 mg/kg BIBR 1048 MS, as compared to control. There were only insignificant effects on respiratory rate, tidal volume, and minute volume at all doses tested.

Cardiovascular investigations were conducted as part of the 4-week toxicity study in conscious rats and further ECG investigations were conducted in the 26- and 52-week toxicity studies in Rhesus monkeys. There was no effect on heart rate or blood pressure with oral doses of 30, 100 or 300 mg/kg in conscious rats. There were also no relevant,

dose-dependent or consistent effects on heart rate, blood pressure, and on electrocardiogram morphology, including PR-interval, QT-interval, and QS-complex width after oral doses up to 200 mg/kg in Rhesus monkeys.

3.2.2 Pharmacokinetics

Absorption

The oral pharmacokinetics of the prodrug dabigatran etexilate mesilate (BIBR 1048 MS) in various animal species (mouse, rat, rabbit and Rhesus monkey) was characterized *in vivo* as having low oral absorption. Once absorbed, BIBR 1048 MS was almost completely cleaved during first-pass metabolism to the active moiety, dabigatran (BIBR 953 ZW). In general, the pharmacokinetics of BIBR 953 ZW after oral dosing of BIBR 1048 MS were almost dose-linear at clinically relevant doses with no consistent effect of gender or repeated dosing.

Distribution

Distribution of BIBR 953 ZW in rats was relatively low, and occurred in most tissues except the CNS. The highest concentrations were found in the liver and urinary tract. Plasma protein binding was low in all species with a range of 22-39%. Low drug concentrations were detected in fetal tissues of pregnant dams, relative to those seen in blood and placenta. Thus, the placental barrier was seen to be somewhat effective at limiting maternal-fetal drug transport.

Metabolism

The cleavage of the prodrug BIBR 1048 MS to the active moiety BIBR 953 ZW by esterase-catalysed hydrolysis was the most prevalent metabolic reaction. The involvement of CYP isoenzymes to the metabolism was minimal. Consistent with this finding, there was neither inhibition nor induction of CYP isoenzymes at therapeutic or supratherapeutic drug concentrations.

BIBR 953 ZW was the predominant drug-related compound in plasma, urine, and feces following both oral administration of BIBR 1048 MS and intravenous administration of BIBR 953 ZW. Beside the active intermediates BIBR 1087 SE and BIBR 951 ZW, and the active moiety BIBR 953 ZW, pharmacologically active acyl-glucuronides of BIBR 953 ZW were identified as additional metabolites, especially in Rhesus monkey and man. The acyl-glucuronides of BIBR 953 ZW (present in man) were also generated in significant amounts in the main animal species (rats and Rhesus monkeys) used in the non-clinical studies. All of the acyl-glucuronide metabolites have been adequately qualified in the non-clinical evaluation.

Excretion

Following oral or intraduodenal administration of radiolabelled BIBR 1048 MS, excretion of drug-related radioactivity ranged between 87-93% in the faeces, 2-11% in the urine, and 0.3-8% in the bile of all species investigated. Following IV administration of radiolabelled BIBR 953 ZW, approximately 40-50% of the drug-related radioactivity was excreted in the urine and about 40% in the faeces (including bile) in the rodent species. However, in the Rhesus monkey up to 80% of the radioactivity was excreted in the urine and about 20% in faeces, after IV dosing. In the rodent species, excretion was fast and almost complete (>90%) within 24 hours, and in the rabbit, excretion was within 72 hours. Enterohepatic circulation was negligible.

3.2.3 Toxicology

The toxic potential of BIBR 1048 MS, known as dabigatran etexilate mesilate, which is the orally non-active prodrug of BIBR 953 ZW, has been investigated in an extensive program of non-clinical studies. The program included single-dose toxicity studies, repeat-dose toxicity studies, genotoxicity/mutagenicity *in vitro* and *in vivo* assays, reproductive and developmental toxicity studies, well as an immunotoxicity study.

Single-Dose Toxicity

The acute oral toxicity of BIBR 1048 MS after oral administration was low. The approximate lethal dose (ALD) was >2,000 mg/kg in mice and rats, and >600 mg/kg in dogs and Rhesus monkeys.

Repeat-Dose Toxicity

In the repeat-dose toxicity studies, up to 26 weeks in rats and up to 52 weeks in Rhesus monkeys, no adverse effects except for pharmacodynamically-mediated bruising and hemorrhages induced by administration of high doses of BIBR 1048 MS were reported. The findings that reflected exaggerated pharmacological effects or compensatory effects showed recovery after discontinuation of treatment. In all animal species used in the non-clinical program, it was noteworthy that no evidence was obtained of adverse effects on the liver. No early signals of hepatotoxicity were detected in rats or Rhesus monkeys.

Genotoxicity and Mutagenicity

In a battery of *in vitro* and *in vivo* studies (including the Ames Bacterial Reversion assay, the mouse lymphoma mutation assays, and the bone marrow micronucleus assays), BIBR 1048 MS and BIBR 953 ZW did not provide evidence of genotoxic/mutagenic potential.

Carcinogenicity

Carcinogenic studies were not provided. This exclusion is justified as the recommended treatment regime does not extend beyond 6 months in duration.

Reproductive and Developmental Toxicity

In the embryo-fetal development and fertility/early developmental toxicity studies in rats, maternal and (early) embryo-fetal toxicity occurred only at the high dose of 200 mg/kg BIBR 1048 MS. Fertility, and the ability to mate and reproduce were not affected by exposure to BIBR 1048 MS at potentially relevant exposures.

The embryo-fetal development toxicity study in rabbits also indicated maternal effects only at the high dose of 200 mg/kg. No teratogenic effects were noted.

In the pre- and post-natal development study in rats, maternal toxicity was observed at 70 mg/kg BIBR 1048 MS due to bleeding episodes into the genital tract during parturition. No drug-related effects on the post-natal development of the offspring were noted, as shown by normal body weight development, normal survival after birth, and normal physical post-natal development.

Local Tolerance

BIBR 1048 MS and BIBR 953 ZW did not provide evidence of local intolerance in the studies provided.

Immunotoxicity

In the immunotoxicological assessment of a 13-week dose study in rats, a slight reduction of splenic lymphocytes was reported which did not appear to be clearly dose-related, in female rats that received 100 and 300 mg/kg BIBR 1048 MS. Male rats did not show similar changes of lymphocyte counts. There was also no histopathological correlate in the spleen of the affected animals. Therefore, this change was not considered to be drug-related. In the other toxicity studies, there was also no presence of histopathological

changes in the bone marrow or the lymphatic organs (thymus, spleen, lymph nodes). The lack of these changes provide evidence of the absence of a drug-related effect of BIBR 1048 MS on the immune system.

3.2.4 Conclusion

Dabigatran (BIBR 953 ZW) is a potent and specific inhibitor of thrombin, demonstrating anti-coagulant and anti-thrombotic activity both *in vitro* and *in vivo*. *In vivo*, it has a relatively wide safety window between anti-thrombotic efficacy and bleeding side effects.

Both the orally administered prodrug, dabigatran etexilate mesilate (BIBR 1048 MS), and its principal active metabolite, BIBR 953 ZW, were generally well tolerated. Few adverse effects were observed in the non-clinical safety studies in mice, rats, guinea pigs, rabbits, dogs, and Rhesus monkeys, except at exceedingly high doses of the administered drug. In general, these effects were directly or indirectly associated with the anticoagulant properties of BIBR 953 ZW, namely an enhanced propensity for bleeding events or relevant compensatory effects at high dose levels, and thus correspondingly, high plasma concentrations of drug.

Based on the non-clinical data, Pradax appears to be a drug with a favourable risk profile, given its evident anticoagulant properties, with good potential for clinical benefit in the treatment and prevention of thrombotic diseases.

3.3 Clinical Basis for Decision

3.3.1 Pharmacodynamics

Dose-escalating studies conducted with patients undergoing primary elective total hip replacement surgery evaluated the pharmacokinetic/pharmacodynamic (PK/PD) characteristics of dabigatran, by determining plasma drug concentrations and coagulation parameter values and correlating these with clinical safety and efficacy. The blood coagulation parameters: activated partial thromboplastin time (aPTT), prothrombin time (PT), as measured by International Normalised Ratio (INR), ecarin clotting time (ECT), and thrombin time (TT) were measured in parallel with the dabigatran plasma concentrations. A correlation between dabigatran plasma levels and the degree of anticoagulant effect, was established as seen by prolongations of aPTT, INR, ECT, and TT. Evidence of a linear relationship was observed between ECT, and TT, whereas aPTT increased in a nonlinear manner with plasma concentrations. A linear relationship between plasma concentration and INR was observed as well, however, this assay lacks sensitivity within a clinically-relevant plasma concentrations range.

3.3.2 Pharmacokinetics

Absorption

Dabigatran etexilate mesilate (the salt form of dabigatran etexilate) was rapidly absorbed and then rapidly converted to its active form, dabigatran. Peak plasma concentrations of dabigatran occurred 1-2 hours after drug administration in healthy volunteers. The time to reach the peak plasma concentration (t_{max}) was delayed to approximately 6 hours in the immediate post-operative orthopaedic surgery patient. Administration of food resulted in an increase of the median t_{max} from 2 to 4 hours post dose, along with an increase in AUC of 27% and C_{max} of 9%.

Distribution

Dabigatran demonstrated low (approx. 35%) and concentration-independent plasma protein binding, resulting in relatively low potential for protein binding displacement interactions. The volume of distribution of dabigatran was 60–70 L, indicating moderate extravascular distribution. The average measured blood cell-plasma ratio of <0.3 demonstrates that dabigatran does not readily penetrate into the red blood cells.

Metabolism

Following oral administration, dabigatran etexilate is rapidly converted by non-specific plasma and hepatic esterases to dabigatran. Dabigatran etexilate was only transiently detectable in plasma. Two intermediates, BIBR 951 CL (an active thrombin inhibitor) and BIBR 1087 SE (inactive), were detectable at very low concentrations for <6 hours following oral dosing of up to 600 mg. Dabigatran is subject to glucuronidation forming pharmacologically active acylglucuronides. The sum of the four dabigatran glucuronide isomers is approximately 20% of the exposure (AUC) of dabigatran.

Excretion

Following an intravenous dose of radiolabelled dabigatran, 85% of the dose was excreted in the urine within 168 hours in healthy male volunteers. An additional 6% was excreted in the faeces, indicative that dabigatran is primarily cleared by the kidneys. The rate of renal clearance of dabigatran was similar to the glomerular filtration rate which suggests that the drug is eliminated via filtration without any net tubular secretion or absorption.

The excretion of dabigatran into human breast milk was not investigated.

Drug Interaction Studies

The *in vitro* investigations demonstrated that the human cytochrome P450 system did not play a major role in the metabolism of dabigatran etexilate, and that dabigatran etexilate (not dabigatran) served as a substrate of P-glycoprotein (P-gp). Potent P-gp inducers or inhibitors may affect dabigatran exposure.

Drug interaction studies were performed to assess the effects of dabigatran with pantoprazole, atorvastatin (CYP 3A4 and P-gp substrate), diclofenac (CYP 2C9 substrate, UGT 2B7 substrate, weak inhibitor of UGT 1A1), digoxin (P-gp substrate), amiodarone (CYP 2C9, 2D6 and 3A4 inhibitor, and P-gp inhibitor), and quinidine (P-gp inhibitor). Concomitant use with potent P-gp inhibitors, e.g. quinidine, is contraindicated.

Special Populations

Elderly Patients
An increase in drug exposure (40-60%) was reported in elderly subjects (>65 years of age) compared to younger subjects.

Renal Impairment
Subjects with renal impairment had substantially higher dabigatran exposure and demonstrated a longer half-life of dabigatran because of lower renal clearance of dabigatran compared with the control group with normal renal function. In subjects with severe renal impairment, dabigatran exposure was approximately 6 times higher, necessitating the contraindication of this drug in this patient population. In patients with moderate renal impairment, administration of dabigatran with dose adjustment would be appropriate. Monitoring of renal function during and before exposure to dabigatran should be considered. The low dabigatran clearance in the uraemic patients was expected because renal excretion is the predominant route of elimination for systemic dabigatran.

Hepatic Impairment
Any differences observed between patients with moderate hepatic impairment and healthy control volunteers in the pharmacodynamic studies were not deemed relevant in respect to the pharmacokinetic or pharmacodynamic properties of dabigatran. However, this data is based on limited numbers of patients studied using a single oral dose of 150 mg dabigatran. The use of dabigatran in patients with moderate or severe hepatic impairment is not recommended as they were excluded from clinical studies.

3.3.3 Clinical Efficacy

The clinical trial database included results from >8,000 patients in three randomized, double-blind, parallel group, pivotal Phase III studies. The dabigatran etexilate dose regimens tested in the each of the Phase III studies were 220 mg once daily (QD), and 150 mg QD, each initiated with a half dose on the day of surgery. Enoxaparin was selected as the comparator for the Phase III studies as it is considered to be the standard therapy for venous thromboembolic events (VTE) prevention following major orthopaedic surgery. Two total knee replacement (TKR) studies were carried out, with the REMODEL study that used enoxaparin 40 mg QD as the comparator regimen conducted primarily in Europe, and the REMOBILIZE study that evaluated enoxaparin 30 mg twice daily (BID) in the United States. Another study called RENOVATE conducted in Europe compared the effects of dabigratan with enoxaparin 40 mg QD in patients undergoing total hip replacement (THR).

All of the pivotal studies in the Phase III programme were non-inferiority studies, and the pre-specified composite primary efficacy endpoint was total VTE and all-cause mortality. The composite of major VTE and VTE-related death was a pre-specified secondary endpoint of each of the Phase III studies, as were also each of the individual components of the two composite endpoints, total VTE and all-cause mortality, and major VTE and VTE-related mortality.

Each of the two European pivotal Phase III studies (REMODEL in TKR and RENOVATE in THR) demonstrated the non-inferiority of both doses of dabigatran etexilate studied compared to enoxaparin, 40 mg QD. For the primary endpoint (total VTE and all-cause mortality) and for the secondary endpoint (major VTE and VTE-mortality), the point estimate for the 220 mg dose of dabigatran etexilate was slightly better than the point estimate for enoxaparin, while for the comparison between 150 mg dabigatran etexilate and enoxaparin, enoxaparin was slightly better. This pattern of slightly better results for dabigatran 220 mg QD compared to enoxaparin and slightly worse results for dabigatran 150 mg QD compared to enoxaparin was maintained through all study protocol pre-specified sensitivity analyses, and therefore is considered a robust finding in these studies. The major bleeding and clinically relevant bleeding results were not materially divergent from these reported efficacy results.

The non-inferiority margin in the rate of total VTE and all-cause mortality (the primary endpoint) was not achieved in REMOBILIZE, the North American TKR study. The difference in total VTE rates in this study was primarily driven by a difference in distal DVT. It should be noted that this TKR study differed from the European TKR study in three potentially important ways. First, the time to first oral study medication dose was later in the North American study (in order to be acceptable for U.S. local practice, the protocol specified the initial dabigatran etexilate dosing window as 6-12 hours post-

surgery compared to 1-4 hours post-surgery for the EU TKR and THR studies). Second, the treatment duration was longer in the North American study than in the European TKR study, at a protocol-specified duration of 12-15 days, rather than 6-10 for the European TKR study, REMODEL. Third, the comparator dose and regimens were different: i.e., enoxaparin 60 mg daily was administered in divided doses in the North American TKR study, compared to 40 mg given once daily for both EU Phase III studies. It is possible that if dabigatran were to be used 1-4 hours post-surgery, rather than 6-12 hours, greater effectiveness in VTE prevention could be expected. Earlier use at 1-4 hours post-surgery, as used in the European studies, should result in an acceptable risk of bleeding, with benefit approaching that of enoxaparin 30 mg BID, and likely equivalent to or better than enoxaparin 40 mg QD in VTE prevention in TKR. In the REMOBILIZE study that used enoxaparin 30 mg BID as a comparator, substantially lower incidences of the VTE endpoints were seen compared to other similar studies that used enoxaparin 40 mg QD. This is in concordance with the clinical reviewer's opinion that enoxaparin 30 mg BID results in meaningfully greater anticoagulant effect relevant to VTE prevention than 40 mg QD.

In summary, dabigatran 220 mg QD given 1-4 hours after elective total knee replacement or total hip replacement is an effective option in the prevention of total VTE, major VTE, and VTE-related death.

3.3.4 Clinical Safety

The safety database included clinical data from 7,942 patients who received at least one dose of dabigatran etexilate. Results were taken from 30 Phase I studies, two Phase II, and three pivotal Phase III studies in the target indication of prevention of VTE in patients undergoing total hip or knee joint replacement surgery. Of the 7,942 patients who received at least one dose of dabigatran etexilate, 5,419 participated in the Phase III primary VTE prevention programme. More than 3,600 patients received at least 10 days of dabigatran etexilate, and >2,000 patients received at least 28 days of dabigatran etexilate to date.

Overall, the occurrence of total adverse events, adverse events leading to study drug discontinuation, and serious adverse events were similar between the study drug and comparator, for both the treatment period and during the 2-3 month extended follow-up period. The only adverse events clearly associated with dabigatran etexilate, and in which a dose response was observed, were those of bleeding or signs of bleeding, which is to be expected for an anticoagulant. The two dosing regimens of dabigatran etexilate in the pivotal trials were not associated with excess bleeding when compared to enoxaparin. A combination of coagulation laboratory assays (e.g., aPTT, thrombin time, etc.) can be

used for a rapid assessment to evaluate if excessive anticoagulant effects of dabigatran are present when severe bleeding occurs. Conservative management including circulatory support with transfusions as needed and diuresis may be recommended.

Dabigatran is excreted primarily through the kidneys. Patients who develop acute renal failure should discontinue Pradax (dabigatran etexilate) therapy as significant drug accumulation can occur. The use of Pradax in patients with severe renal impairment is contraindicated. There is evidence of a linear relationship between degree of renal impairment and plasma concentration of dabigatran following oral administration of dabigatran etexilate. Accordingly, caution should be employed when Pradax is to be used in patients with moderate renal impairment. The degree of renal impairment may be expected to affect the pharmacodynamic effect, along with the risk of bleeding, therefore a baseline assessment of renal function should be undertaken before the initiation of treatment. Furthermore, during treatment periodic monitoring of renal function is advised since dosage adjustments or discontinuation of the study drug may need to be undertaken.

3.4 Benefit/Risk Assessment and Recommendation

3.4.1 Benefit/Risk Assessment

Adequate evidence was submitted to demonstrate the effectiveness of Pradax 220 mg once daily when given orally 1-4 hours after major orthopaedic surgery, in both total knee replacement and total hip replacement in the prevention of total VTE, major VTE, and VTE-related death. A lower dose of Pradax, namely 150 mg once daily, should be considered in patients over the age of 75 years, and should be used in all patients with moderate renal impairment, since these patients have been shown to have elevations in serum concentrations of dabigatran, which may be accompanied with an enhanced risk of bleeding. Use in severe renal impairment is contraindicated due to markedly increased exposure to dabigatran and the consequent increased risk of bleeding.

The only clearly identified safety risk associated with dabigatran etexilate is, as expected, a dose-related increase in total bleeding and major bleeding. Given the effectiveness of Pradax that was demonstrated in prevention of VTE-related adverse events following major orthopedic surgery, the absolute increase in bleeding is not considered materially different from that seen with enoxaparin, the standard comparator treatment used.

In conclusion, Pradax appears to be a useful oral treatment for the prevention of VTE following major orthopedic surgery in patients without severe renal impairment.

3.4.2 Recommendation

Based on the Health Canada review of data on quality, safety and effectiveness, Health Canada considers that the benefit/risk profile of Pradax is favourable in the prevention of venous thromboembolic events in patients who have undergone elective total hip replacement or total knee replacement surgery treatment. The New Drug Submission complies with the requirements of sections C.08.002 and C.08.005.1 and therefore Health Canada has granted the Notice of Compliance pursuant to section C.08.004 of the *Food and Drug Regulations*.

4 SUBMISSION MILESTONES

Submission Milestone	Date
Pre-submission meeting	2007/06/05
Submission filed	2007/06/19
Screening 1	
Screening Deficiency Notice issued	2007/08/01
Response filed	2007/08/10
Screening Acceptance Letter issued	2007/08/16
Review 1	
Biopharmaceutics Evaluation complete	2008/01/11
Quality Evaluation complete	2008/06/09
Clinical Evaluation complete	2008/06/10
Labelling Review complete	2008/05/28
NOC issued by Director General	2008/06/10