Summary Basis of Decision (SBD)
PrVOTRIENT™
Pazopanib hydrochloride, 200 mg and 400 mg tablets
GlaxoSmithKline Inc.
Submission Control Number: 128332

Date Issued: 2010/12/07

Health Products and Food Branch
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*Health Canada*

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- minimizing health risk factors to Canadians while maximizing the safety provided by the regulatory system for health products and food; and,
- 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), **P**VOTRIENT**MC** chlorhydrate de pazopanib, 200 mg et 400 mg, comprimés, GlaxoSmithKline Inc. Numéro de contrôle de la présentation : 128332
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 (AE), 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 ............................................................... 1

2 NOTICE OF DECISION ................................................................................................. 2

3 SCIENTIFIC AND REGULATORY BASIS FOR DECISION ......................................... 3

3.1 Quality Basis for Decision ......................................................................................... 3

3.1.1 Drug Substance (Medicinal Ingredient) ............................................................... 3

3.1.2 Drug Product ........................................................................................................ 4

3.1.3 Facilities and Equipment ..................................................................................... 6

3.1.4 Adventitious Agents Safety Evaluation ................................................................. 6

3.1.5 Conclusion............................................................................................................ 6

3.2 Non-clinical Basis for Decision .................................................................................. 6

3.2.1 Pharmacodynamics .............................................................................................. 6

3.2.2 Pharmacokinetics ............................................................................................... 7

3.2.3 Toxicology ............................................................................................................ 8

3.2.4 Conclusion .......................................................................................................... 10

3.3 Clinical Basis for Decision ....................................................................................... 10

3.3.1 Pharmacodynamics ............................................................................................ 10

3.3.2 Pharmacokinetics ................................................................................................ 11

3.3.3 Clinical Efficacy .................................................................................................. 12

3.3.4 Clinical Safety .................................................................................................... 14

3.3.5 Additional Issues .................................................................................................... 16

3.4 Benefit/Risk Assessment and Recommendation ....................................................... 16

3.4.1 Benefit/Risk Assessment ..................................................................................... 16

3.4.2 Recommendation ................................................................................................ 17

4 SUBMISSION MILESTONES ......................................................................................... 18
1 PRODUCT AND SUBMISSION INFORMATION

Brand Name: PrVOTRIENT™
Manufacturer/Sponsor: GlaxoSmithKline Inc.
Medicinal Ingredient: Pazopanib hydrochloride
International Non-proprietary Name: Pazopanib hydrochloride
Strengths: 200 mg and 400 mg
Dosage form: Tablet
Route of Administration: Oral
Drug Identification Numbers (DINs): 02352303 - 200 mg
02352311 - 400 mg
Therapeutic Classification: Antineoplastic agent
Non-medicinal Ingredients: Hypromellose, macrogol 400, magnesium stearate, microcrystalline cellulose, povidone (K30), polysorbate 80, sodium starch glycollate, titanium dioxide (E171), iron oxide black (E172) and iron oxide yellow (E172)
Submission Type and Control Number: New Drug Submission,
Control Number: 128332
Date of Submission: 2009/06/16
Date of Authorization: 2010/05/27

TM VOTRIENT, used under license by GlaxoSmithKline Inc.
2 NOTICE OF DECISION

On May 27, 2010, Health Canada issued a Notice of Compliance to GlaxoSmithKline Inc. for the drug product Votrient™.

Votrient™ contains the medicinal ingredient pazopanib hydrochloride which is an antineoplastic agent.

Votrient™ is indicated for the treatment of patients with metastatic renal cell (clear cell) carcinoma (mRCC) who have received no prior systemic therapies or who have received prior treatment with cytokines for metastatic disease. Approval of Votrient™ is based on significant progression-free survival (PFS) benefit in patients with mRCC of good performance status [Eastern Cooperative Oncology Group (ECOG) grade 0-1]. Prolongations of overall survival was not demonstrated nor were quality-of-life differences shown between patients receiving Votrient™ versus placebo in the pivotal phase III trial.

Votrient™ is a multi-tyrosine kinase inhibitor. It is an inhibitor of vascular endothelial growth factor receptors -1, -2, and -3, platelet-derived growth factor-α and -β, and stem cell factor receptor. As a result, Votrient™ may help prevent the growth of new blood vessels needed for solid tumours to grow.

The market authorization was based on quality, non-clinical, and clinical information submitted. In support of the proposed indication, a Phase III, randomized, double-blind, placebo-controlled, multicentre study was submitted to evaluate the efficacy and safety of Votrient™ compared to placebo in patients with mRCC. A total of 435 patients were randomized 2:1 to receive Votrient™ 800 mg once daily or placebo. The primary objective of the study was to evaluate and compare the two treatment arms for PFS. Disease assessments were performed every 6 weeks until Week 24, and subsequently every 8 weeks thereafter until disease progression. Results indicated that PFS was longer in patients treated with Votrient™ compared to patients treated with a placebo (median PFS was 9.2 months in the Votrient™ treatment group versus 4.2 months in the placebo treatment group). Clinically significant adverse events associated with Votrient™ include hepatotoxicity, hypertension, QT/QTc prolongation and torsade de pointes, arterial thrombotic events, hemorrhagic events, and gastrointestinal perforation and fistula.

Votrient™ (200 mg and 400 mg, pazopanib hydrochloride) is presented in tablet form. The recommended dose of Votrient™ is 800 mg taken once daily. Votrient™ should be taken orally without food and at least one hour before or two hours after a meal. Dose modifications should be in 200 mg increments in a stepwise fashion based on individual tolerability in order to manage adverse reactions. The dose of Votrient™ should not exceed 800 mg. Further dosing guidelines are available in the Product Monograph.
Votrient™ is contraindicated for patients who are hypersensitive to Votrient™ (pazopanib hydrochloride) or to any ingredient in the formulation or component of the container. Hepatotoxicity is an important safety concern in patients taking Votrient™. Hepatic function needs to be closely monitored and dosing interrupted, reduced or discontinued as recommended in the Product Monograph. Votrient™ is not recommended for patients that have baseline plasma bilirubin concentrations greater than 1.5 times the upper limit of normal (ULN) (with direct bilirubin greater than 35%) and alanine aminotransferase elevations greater than 2 times ULN, or who have moderate or severe hepatic impairment (Child Pugh B and C). Votrient™ 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 Votrient™ are described in the Product Monograph.

Based on the Health Canada review of data on quality, safety, and efficacy, Health Canada considers that the benefit/risk profile of Votrient™ is favourable for the indication stated above.

3 SCIENTIFIC AND REGULATORY BASIS FOR DECISION

3.1 Quality Basis for Decision

3.1.1 Drug Substance (Medicinal Ingredient)

General Information

Pazopanib hydrochloride, the medicinal ingredient of Votrient™, is an antineoplastic agent. Votrient™ is a tyrosine kinase inhibitor of vascular endothelial growth factor (VEGF) receptors (VEGFR) -1,-2 and -3, platelet-derived growth factor receptors (PDGFR) -α and -β and stem cell factor receptor c-KIT. The inhibition of these proteins may prevent the growth of new blood vessels needed for solid tumours to grow.

Manufacturing Process and Process Controls

Pazopanib hydrochloride is manufactured via a multi-step synthesis. Each step of the manufacturing process is considered to be controlled within acceptable limits.

The materials used in the manufacture of the drug substance are considered to be suitable and/or meet standards appropriate for their intended use.
Characterization

The structure of pazopanib hydrochloride has been adequately elucidated and the representative spectra have been provided. Physical and chemical properties have been described and are satisfactory.

Appropriate tests are adequately controlling the levels of product- and process-related impurities.

Control of Drug Substance

Copies of the analytical methods and, where appropriate, validation reports were provided for all analytical procedures used for release and stability testing of pazopanib hydrochloride. The specifications are considered acceptable for the drug substance. Data from the batch analyses were reviewed and are within the proposed acceptance criteria.

The proposed packaging components are considered acceptable.

Stability

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

3.1.2 Drug Product

Description and Composition

Votrient™ is an immediate-release tablet containing either 200 mg or 400 mg of pazopanib free base as pazopanib hydrochloride.

The 200 mg tablets of Votrient™ are modified capsule-shaped, grey, film-coated tablets with GS JT debossed on one side, and are available in bottles of 30 tablets, 90 tablet, and 120 tablets.

The 400 mg tablets of Votrient™ are modified capsule-shaped, yellow, film-coated tablets with GS UHL debossed on one side, and are available in bottles of 30 tablets and 60 tablets. The Votrient™ 400 mg tablets are not available in Canada.
The non-medicinal ingredients (excipients) in the tablet core are magnesium stearate, microcrystalline cellulose, povidone (K30), and sodium starch glycollate. The excipients in the tablet coating are hypromellose, iron oxide black (E172, 200 mg tablet), iron oxide yellow (E172, 400 mg tablet), macrogol, polysorbate 80, and titanium dioxide (E171).

All excipients found in the drug product are acceptable for use in drugs according to the Food and Drug Regulations. The compatibility of pazopanib hydrochloride 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**

The method of manufacturing is considered acceptable and the process is considered adequately controlled within justified limits.

**Control of Drug Product**

Votrient™ is tested to verify that its identity, appearance, content uniformity, assay, dissolution, particle size, weight, thickness, friability, moisture content, levels of degradation products, residual solvents, and drug-related impurities are within acceptance criteria. The test specifications and analytical methods are considered acceptable; the shelf-life and the release limits, for individual and total degradation products, are within acceptable limits.

Data from final batch analyses were reviewed and are considered to be acceptable according to the specifications of the drug product. The validation process is considered to be complete.

**Stability**

Based on the real-time, long-term, accelerated, and stressed stability data submitted, the proposed 24-month shelf-life at 15-30°C for Votrient™ is considered acceptable when the tablets are packaged in a high-density polyethylene bottle with a polypropylene child-resistant closure and sealed with a polyethylene-faced foil induction heat seal liner.
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 design, operations, and controls of the facility and equipment that are involved in the production of Votrient™ are considered suitable for the activities and products manufactured.

The site is rated Good Manufacturing Practices (GMP) compliant for the manufacturing activities.

### 3.1.4 Adventitious Agents Safety Evaluation

Not applicable. The excipients used in the drug product formulation are not from animal or human origin.

### 3.1.5 Conclusion

The Chemistry and Manufacturing information submitted for Votrient™ 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

#### 3.2.1 Pharmacodynamics

The pharmacology of pazopanib has been characterized in vitro and in vivo. Pazopanib exerts its pharmacological activity by inhibiting angiogenic signaling pathways through a panel of growth factors and receptors, primarily the VEGF receptor (VEGFR) family. Inhibition of these growth factors and/or their receptors results in the inhibition of neovascularization, disruption of existing tumor vascularization, and inhibition of proangiogenic growth factor release.

In vitro, pazopanib potently inhibited phosphorylation of VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-α, PGDFR-β and the stem cell factor receptor c-Kit. In vivo, pazopanib
inhibited VEGF-induced VEGFR-2 phosphorylation in the lungs of mice, angiogenesis in various animal models, and the growth of some human tumour xenografts in mice.

Safety Pharmacology

Single oral doses of 300 mg/kg pazopanib did not cause any effects on the respiratory or nervous system in rats.

Pazopanib exhibited no significant effects on QTc interval length and no evidence of drug-related electrocardiogram (ECG) waveform abnormalities or arrhythmias in cardiovascular studies in which monkeys were given a single oral dose of 500 mg/kg or a single intravenous (IV) dose of 3.75 mg/kg. Following the IV dose, the average maximum plasma concentration (C_{max}) was 55.24 \mu g/mL, approximately twice the clinical level in patients.

3.2.2 Pharmacokinetics

The non-clinical pharmacokinetics (PK) of pazopanib has been comprehensively evaluated in the species used in the toxicity studies. The species used (rat, mouse, dog, and monkey) are appropriate models for the evaluation of human safety.

Absorption

Pazopanib demonstrated a rapid absorption in mice and rats. The mean oral bioavailability was 72% and 61% in Wistar rats and Sprague Dawley rats, respectively. In monkeys, the oral bioavailability ranged from a mean of 16% to 53%, and the systemic exposure was less than proportional as the dose was increased (for example [e.g.], a 10-fold increase in dose resulted in a 6-fold increase in exposure).

The effect of food on the PK of pazopanib was species-dependent. In the fed-state, pazopanib plasma concentrations were decreased in dogs; however in monkeys, there was no apparent effect of food on absorption and/or elimination.

Distribution

Pazopanib was highly plasma protein bound in all species tested with only a minor association with blood cells. In human plasma, the percentage of protein-bound drug was greater than 99.9% at all concentrations, which was highest amongst all samples tested.
In mouse and monkey plasma, the percent protein-bound values were greater than 99.7% and 99.8%, respectively. In rat and dog plasma, the percent protein-bound values were greater than 99.5% and 98.8%, respectively.

In a quantitative tissue distribution study in rats, single doses of radiolabelled pazopanib were administered. Pazopanib was widely distributed into the tissues showing the highest concentrations at 2-hours post-dose with most tissues. Tissues with high concentrations included the meninges, liver, adrenal medulla, lung, aorta, cecum, stomach, and small intestine. An association of pazopanib to melanin was identified.

**Metabolism**

The *in vitro* and *in vivo* metabolism of pazopanib was qualitatively similar in all species tested. Pazopanib was primarily metabolized to mono and di-oxygenated species. An *in vitro* study using human liver microsomes demonstrated that this oxidative metabolism was primarily mediated by the cytochrome P450 (CYP) 3A4 isozyme, with minor contributions from CYP1A2 and CYP2C8. Unchanged pazopanib was the principal component in human plasma. There were no unique human metabolites reported.

**Excretion**

Faecal excretion was the predominant route of elimination in monkeys and rats. In monkeys, faecal excretion accounted for 85.0% and 86.7% of the dose in males and females, respectively. In rats, it accounted for approximately 61% and 52% of the dose in males and females, respectively. Pazopanib was predominately eliminated as unchanged pazopanib in the faeces. The metabolites of pazopanib were also eliminated largely via the faeces rather than urine.

**3.2.3 Toxicology**

An adequate toxicology program for pazopanib was conducted to support the proposed indication for the treatment of metastatic renal cell cancer. Most of the toxicology studies were performed using the micronized monohydrochloride salt, the form intended for clinical use. The toxicology studies were conducted according to acceptable scientific standards and the majority of studies and all pivotal studies were compliant with Good Laboratory Practices (GLP).
Single-Dose Toxicity

In acute toxicity studies, no deaths or significant findings were reported in rats following single IV injections of 1.1 or 5.4 mg/kg pazopanib, or in dogs following a single oral dose of ≤450 mg/kg pazopanib.

Repeat-Dose Toxicity

The principal non-clinical toxicology findings associated with oral pazopanib administration in rats included effects on bone, teeth, nail beds, reproductive organs, haematological tissues, liver, kidney, adrenal glands, and pancreas. Most of these effects occurred with doses ≥30 mg/kg, however effects on the kidney and adrenal glands occurred at ≥3 mg/kg. The hypertrophy of epiphyseal growth plates, nail abnormalities (including broken, overgrown, or absent nails) and tooth abnormalities in growing incisor teeth (including excessively long, brittle, broken and missing teeth, as well as dentine and enamel degeneration and thinning) that were observed in rats provide paediatric implications for growing bones and nails. Therefore, Votrient™ is not recommended for use in children.

Many of the treatment-related findings in the rodent repeat-dose toxicology studies may relate to pharmacologically-mediated changes as a result of VEGFR inhibition and/or disruption of VEGF signaling pathways. Similar changes have been observed with other drugs in this class.

The recommended human therapeutic dose of pazopanib (800 mg/day or 16 mg/kg based on a 50 kg adult) is not expected to be associated with many of the observed rodent pharmacologic responses (e.g. teeth and bone effects). The local deposition of pazopanib in intestines and associated lymph nodes that occurred in monkeys and rodents following oral administration of large quantities of pazopanib may not be relevant to humans administered 800 mg/day; however, diarrhoea is a common adverse reaction in humans taking pazopanib. Hepatic and renal/urinary effects noted in rodents have also been observed in humans.

Genotoxicity

Pazopanib was not genotoxic in vitro or in vivo. Genotoxicity was evaluated in bacteria (Ames assay) at doses up to 5000 μg/plate, in human peripheral lymphocytes (chromosome aberration assay) at concentrations up to 200 μg/mL, and in rat (micronucleus assay) at doses up to 2000 mg/kg.
Carcinogenicity

No rodent carcinogenicity studies were performed; however, a low incidence of potentially pre-neoplastic findings (eosinophilic foci in 2/12 females) and one neoplasm (hepatocellular adenoma in 1/12 females) were present in the liver of mice administered 1000 mg/kg for 13 weeks (AUC in female mice 2.3-fold the human AUC at 800 mg). Therefore, the potential risk for carcinogenicity in humans is unknown.

Reproductive and Developmental Toxicity

Fertility was decreased in female rats that were administered 300 mg/kg pazopanib. Maternal and foetotoxicity occurred in pregnant rats and rabbits, and teratogenicity was observed in rats at systemic exposure levels lower than for human patients. Votrient poses significant risks to women of childbearing age and should be apprised of the potential of foetal harm. The medication should not be taken by women who are pregnant or breast-feeding.

3.2.4 Conclusion

The non-clinical pharmacology, safety pharmacology, pharmacokinetic, and toxicology studies have characterized the non-clinical profile of panzopanib in sufficient detail to support the intended use of Votrient™ for the clinical indication. The findings in the toxicology studies are generally consistent with other marketed tyrosine kinase inhibitors for this target. The toxicology studies in rodents showed hypertrophy of epiphyseal growth plates and abnormalities in growing incisors, and therefore Votrient™ is not recommended for use in children. Appropriate warnings and precautionary measures are in place in the Product Monograph to address the identified safety concerns.

3.3 Clinical Basis for Decision

3.3.1 Pharmacodynamics

Votrient™ is an inhibitor of VEGFR-1,-2 and -3 and PDGFR-α and -β. In a Phase I dose-finding study, 800 mg was chosen as the daily dose for subsequent clinical studies. A maximum tolerated dose was not determined. At this dose, >93% of the patients achieved a target trough plasma concentration of 15-20 μg/mL which was similar to the trough concentrations required for efficacy in the non-clinical models and correlated with a 50% probability of observing a study-specific definition of a significant increase in blood
pressure, a proposed pharmacodynamic marker for VEGF inhibition. The 800 mg daily dose correlated with a tolerable safety profile. A slight trend towards an increase in the incidence and severity of hypertension was observed as the dose was increased.

In a Phase II study, oral doses of 800 mg daily resulted in a decrease in soluble VEGFR2. Phase I study results with Dynamic-contrast MRI (DC-MRI) showed a ≥50% decrease in tumour perfusion for 10 of 11 patients who received doses of ≥800 mg. A study evaluating the effect of pazopanib on QTc duration is ongoing in subjects with cancer with results expected in the last quarter of 2010. The sponsor has been requested to provide to Health Canada the final results of the QT study as a post-marketing commitment.

3.3.2 Pharmacokinetics

Absorption

The oral bioavailability of pazopanib reflects absorption that is limited by solubility and reaches saturation at doses above 800 mg once daily. Votrient™ has non-linear kinetics and proportionally less drug is absorbed as the dose is increased. The 800 mg daily dose resulted in approximately a 1.5-fold greater drug exposure than that obtained with the 400 mg daily dose. The drug also displays marked inter-patient variability. Oral absorption increased when the drug was administered with food. It is recommended to administer pazopanib on an empty stomach, at least 1 hour before or 2 hours after a meal.

Distribution

Pazopanib showed a high affinity for protein binding. In human plasma, the percentage of protein-bound drug was >99.9% at all concentrations tested (2.4 to 100 μg/mL).

Metabolism

The oxidative metabolism of pazopanib was primarily mediated by CYP3A4, with minor contributions from CYP1A2 and CYP2C8. Systemic exposure to pazopanib is likely to be altered by inhibitors and inducers of CYP3A4. It is recommended that the concomitant use of strong CYP3A4 inhibitors be avoided as such drugs may increase plasma pazopanib concentrations and cause toxicity.

Metabolites are produced in low abundance and are unlikely to contribute to the biological activity of pazopanib.
Excretion

Most of the administered dose (60-70%) was excreted as unchanged drug in the faeces. Approximately 7-15% of the administered dose was recovered as metabolites in the faeces. Less than 4% of the administered dose was excreted in the urine.

Hepatic Impairment Study

Patients with moderately impaired hepatic function (defined as having a total bilirubin between >1.5 times and 3 times the upper limit of normal [ULN]) had dose-limiting toxicity at a 400 mg daily oral dose, which is half the recommended starting dose. Patients with moderate and severe hepatic impairment should not receive Votrient™ given the potential for hepatotoxicity and the availability of alternative therapies for mRCC.

3.3.3 Clinical Efficacy

The efficacy of Votrient™ in patients with mRCC who were treatment naïve or who received one prior cytokine-based systemic therapy was evaluated in a randomized, international (no North American sites), multicentre, double-blind placebo-controlled Phase III study. Patients were randomized 2:1 to receive Votrient™ (290 patients) or placebo (145 patients), respectively. Of the 435 patients enrolled, 233 patients had received no prior systemic therapy and 202 had received one prior cytokine-based therapy.

Patients were stratified according to prior treatment with cytokines or not (treatment naïve), prior nephrectomy, and Eastern Cooperative Oncology Group (ECOG) performance status. Patients were assigned to treatment groups by central randomization without stratification by centre/site leading to an imbalance in the treatment groups for different centre/country sites. A statistical consult was asked to determine if the central randomization without stratification by centre was appropriate or whether the imbalance in treatment groups compromised the study as a result of differences in patient care and/or study conduct between centre/country sites. The statistical consult found that the imbalance in centre/country sites between treatment groups did not negatively impact the findings from this pivotal study.

The primary efficacy endpoint was progression-free survival (PFS) assessed by an independent review committee. Secondary efficacy endpoints included overall survival (OS), response rate (RR), and quality-of-life (QoL). Patients in the placebo arm were permitted to crossover to Votrient™ at disease progression. Votrient™ reduced the risk of
disease progression or death by 54% (hazard ratio [HR]: 0.46; 95% confidence interval [CI]: 0.34 to 0.62) with a 5-month improvement in median PFS (9.2 months versus 4.2 months for the Votrient™ and placebo treatment arms, respectively). Multiple sensitivity analyses on PFS confirmed the robustness of this analysis. Similar treatment effects were observed in the treatment-naïve and cytokine-pretreated subgroups. An interim analysis of OS (based on 176 deaths) demonstrated a trend favouring the Votrient™ arm compared to the placebo arm (hazard ratio (HR): 0.73; 95% confidence interval (CI): 0.53 to 1.00; one-sided probability (p) =0.020). However, this difference was not statistically significant as it did not meet the pre-specified interim O’Brien-Fleming error spending boundaries (p<0.004) for superiority, and the results were premature. The primary OS analysis is still pending and will be conducted when 287 deaths have accrued; however, these results will be confounded due to protocol-specified potential for crossover of placebo-treated patients to Votrient at progression. The sponsor has been requested to provide to Health Canada the primary OS analysis results as a post-marketing commitment. The RR, defined as the percentage of patients who achieved either a confirmed complete response or partial response according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria, was significantly higher in the Votrient™ arm (30%) compared to the placebo arm (3%). QoL assessments (EORTC QLQ-C30 and EuroQoL EQ-5D) showed no difference between treatment with pazopanib or placebo (p>0.05), indicating no improvement in QoL for patients receiving Votrient™.

Of concern was the observation that a large percentage of patients were censored in each treatment arm before the end of the study (30% in each arm). Differences in reasons for censoring between the two arms were also observed. The sponsor conducted additional sensitivity analyses to account for any possible informative censoring. These analyses supported the primary efficacy analysis results.

In summary, the Phase III study demonstrated benefits in PFS and RR in the Votrient™ treatment arm but no benefits in OS or QoL. The study design to allow patients in the placebo arm to cross-over immediately at progression may impact the ability of the sponsor to detect any improvement in OS in the Votrient™ treatment arm in the final OS analysis.

In a Phase II study, which included patients from North America, the RR for the overall population (number [n] =225) and the United States subgroup (n=63) were similar to that for the Votrient-treated patients in the Phase III study. In the Phase II study, the median PFS in the United States subgroup was similar to that in the non-United States subgroup. These observations suggest that the results from the pivotal Phase III study are generalizable to the North American (including the Canadian) population.
3.3.4 Clinical Safety

The safety of Votrient™ was primarily evaluated in the pivotal Phase III study described in section 3.3.3 Clinical Efficacy. In the pivotal, double-blind, placebo-controlled Phase III study, 435 mRCC patients were randomized to receive Votrient™ or placebo. The median duration of treatment was 7.4 months for patients who received Votrient™ (290 patients) and 3.8 months for the placebo arm (145 patients). Forty-two percent (42%) of the patients that received Votrient™ required a dose interruption and thirty-six percent (36%) required a dose reduction. Adverse events (AEs) leading to permanent discontinuation of the investigational product were reported for 44 (15%) patients in the Votrient™ arm and for 8 (6%) patients in the placebo arm. Four deaths (1.4%) in the Votrient™ arm were determined by the investigators to be directly related to the study drug. The causes of death were abnormal hepatic function, ischemic stroke, and peritonitis.

Hepatotoxicity was observed in the pivotal trial. Hepatic-related laboratory events were the most common reasons for study discontinuation due to AEs (3.8%). Elevated levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin (all grades) occurred in 53%, 53%, and 36% of the patients treated with Votrient™, respectively; compared to 22%, 19%, and 10%, in the placebo arm, respectively. ALT grade 3 or 4 elevations were observed in 12% of patients in the Votrient™ arm compared to 1% of patients in the placebo arm. AST grade 3 or 4 elevations were observed in 8% (grade 3 = 7% and grade 4 = <1%) of patients in the Votrient™ arm compared to <1% in the placebo arm.

Patients with total bilirubin levels >1.5 times the ULN and ALT >2 times the ULN were excluded from clinical studies. Votrient™ is not recommended for patients that have baseline plasma bilirubin concentrations >1.5 times the ULN (with direct bilirubin >35%) and ALT elevations of >2 times the ULN, or who have moderate or severe hepatic impairment (Child Pugh B and C). A study in patients with moderate hepatic impairment demonstrated dose-limiting toxicity at 400 mg. Careful monitoring of hepatic function (every 3-4 weeks) is important, and exclusion of patients with hepatic impairment is essential to allow Votrient™ to be used safely.

Hypertension should be well controlled before taking Votrient™. In the pivotal study, 40% of patients receiving Votrient™ became hypertensive compared to only 10% in the placebo arm. A similar number of patients became hypertensive on Votrient™ in the open-label Phase II study. One case of hypertensive crisis was observed during the
pivotal study with Votrient™ highlighting the need to carefully monitor this event during the course of drug treatment so appropriate antihypertensive medication is prescribed in addition to any dose reductions and interruptions.

Patients with an arterial thrombotic event within 6 months were excluded from participating in the pivotal study during screening. In the pivotal study there were 5 myocardial infarctions (1.7%), 4 ischemic attacks (1.4%) and a single cerebral vascular event (0.3%) in patients receiving Votrient™. No events were recorded in patients on the placebo arm. Pazopanib should be used with caution in patients who are at increased risk for these events. A treatment decision should be made based upon the assessment of individual patient’s benefit/risk.

More haemorrhagic events were observed in patients receiving Votrient™ (13%) compared to patients receiving best supportive care (5%) in the pivotal Phase III study. The most common haemorrhagic events in the patients treated with Votrient™ were haematuria (4%), epistaxis (2%), haemoptysis (2%), and rectal haemorrhage (1%). Pazopanib is not recommended in patients who have a history of haemoptysis, cerebral, or clinically significant gastrointestinal (GI) haemorrhage in the past 6 months. Pazopanib should be used with caution in patients with significant risk of haemorrhage.

In clinical studies for Votrient™ events of QT prolongation (1%) or torsade de pointes (0.3%) have occurred. Votrient™ should be used with caution in patients with a history of QT interval prolongation, patients taking antiarrhythmics or other medications that may potentially prolong QT interval, or those with relevant pre-existing cardiac disease. As noted in section 3.3.1, a study evaluating the effect of pazopanib on QTc duration is currently ongoing; results of which will be submitted to Health Canada when available.

In clinical studies for Votrient™ events of gastrointestinal (GI) perforation or fistula have occurred, some of which were fatal. Votrient™ should be used with caution in patients at risk for GI perforation or fistula.

The above events have been included in a Serious Warnings and Precaution box in the Product Monograph.

The clinical studies did not evaluate left ventricular ejection fraction (LVEF). However, LVEF decreases have been observed in association with pazopanib use in clinical studies with this drug and have been reported with other tyrosine kinase inhibitors. Other important AEs associated with Votrient™ use include hypothyroidism, proteinuria, pancreatitis, diarrhea and fatigue.
3.3.5 Additional Issues

A risk management plan was provided with this new drug submission and was reviewed by the the Marketed Health Products Directorate (MHPD). Advice from MHPD resulted in labelling recommendations to the Product Monograph, and recommendations for post-marketing surveillance activities. These recommendations were communicated to the sponsor and will be developed by the sponsor with MHPD after issuance of the Notice of Compliance.

3.4 Benefit/Risk Assessment and Recommendation

3.4.1 Benefit/Risk Assessment

Canadian clinical experts were consulted during the assessment of the clinical efficacy and safety of Votrient™. The advice received was taken into account in the final conclusions and decisions made by Health Canada.

The efficacy and safety of Votrient™ were evaluated in a Phase III, randomized placebo-controlled international study in patients with mRCC who were treatment-naïve or had received prior cytokine therapy. Patients treated with Votrient™ showed a significant improvement in PFS compared to patients treated with placebo arm. Votrient™ prolonged the median PFS by 5 months compared to placebo. The drug also significantly reduced tumour volume. The overall response rates were 30% and 3% for Votrient™ and placebo, respectively. However, improvement in OS (based on immature data) or quality of life for patients taking Votrient™ was not demonstrated in the pivotal Phase III study. The primary OS analysis will be provided when available as a post-marketing commitment.

The efficacy of Votrient™ compared to other agents currently used for patients with mRCC who had received prior cytokine therapy remains unknown, as the Phase III study used a placebo comparator. At the time the study was conducted, Sutent® was approved in several jurisdictions for first-line treatment of mRCC; however, the sponsor could not attain sufficient supplies of Sutent® to initiate a proper head-to-head comparator trial at that time. A study with Sutent® as a comparator drug is now ongoing.

As the Phase III study did not include any North American sites, extrapolation of these study results to the Canadian population was considered appropriate. This decision was based on the observations that the response rates observed in a Phase II study with North American patients were consistent with those obtained from non-North American patients in that same study and with those in the Votrient™-treated patients in the Phase III study.
Votrient™ will not be appropriate for all patients with mRCC and important safety issues are associated with this drug. Patients should have adequate liver function (normal or mildly impaired only) and well-controlled hypertension before Votrient™ is administered. Proper monitoring of the mRCC patient population is critical to ensure proper dose reductions and interruption in drug therapy, as serious adverse events (SAEs) can occur. SAEs associated with Votrient™ include hepatoxicity, hypertension, QT/Qtc prolongation, arterial thrombotic events, cardiac dysfunction, haemorrhagic events, and gastrointestinal perforation. It is considered important that prescribers are clearly informed of the risk of hepatotoxicity and measures be implemented to mitigate this risk. The Product Monograph emphasizes the risk of hepatotoxicity and its mitigation measures, in addition to information on the other serious toxicities, included in the Serious Warnings and Precautions box and other relevant sections.

Despite the safety issues with Votrient™, including hepatotoxicity, Votrient™ offers another therapy that has an appropriate risk-benefit profile for the treatment of patients with mRCC who have received no prior systemic therapies or who have received prior treatment with cytokines for metastatic disease.

### 3.4.2 Recommendation

Based on the Health Canada review of data on quality, safety and efficacy, Health Canada considers that the benefit/risk profile of Votrient™ is favourable for the treatment of patients with mRCC who have received no prior systemic therapies or who have received prior treatment with cytokines for metastatic disease. 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

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