Health Canada Santé Canada

SUMMARY BASIS OF DECISION (SBD)

Pr APTIVUS®

Tipranavir, 250 mg, capsule

Boehringer Ingelheim (Canada) Ltd.

Submission Control No. 098651

Date Issued	2006/08/15

Health Products and Food Branch

Canada

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maintain and improve their health.
Health Canada

HPFB's Mandate is to take an integrated approach to the management of the risks and benefits to health related to health products and food by:

- 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), ^{Pr}APTIVUS®, Tipranavir, 250 mg, capsule, Boehringer Ingelheim (Canada) Ltd. N^{o} de contrôle de la présentation 098651

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 reviewer 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'.

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1 PRODUCT AND SUBMISSION INFORMATION

Brand Name	[Pr]APTIVUS®
Manufacturer/Sponsor	Boehringer Ingelheim (Canada) Ltd.
Medicinal Ingredient	Tipranavir
International Non-proprietary Name	Tipranavir
Strength	250 mg
Dosage form	Capsule
Route of Administration	Oral
DIN	02273322
Pharmaco-therapeutic group (ATC Code)	Non-Peptidic Protease Inhibitor
Non-medicinal Ingredients	**Non-medicinal ingredients**: Cremophor® EL, ethanol, mono/diglycerides of caprylic/capric acid, propyl gallate, propylene glycol, purified water, and trometamol. **Capsule shell**: gelatin, iron oxide red, propylene glycol, purified water, 'sorbitol special glycerin blend' (d-sorbitol, 1,4-sorbitan, mannitol and glycerin) and titanium dioxide. **Black printing ink**: ammonium hydroxide, ethyl acetate, iron oxide black, isopropyl alcohol, Macrogol, polyvinyl acetate phthalate, propylene glycol, purified water and SDA 35 alcohol
Submission Type and Control No.	New Drug Submission, Control No. 098651
Date of Submission	2005/05/09
Date of Authorization	2005/11/21

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2 NOTICE OF DECISION

On November 21, 2005, Health Canada issued a Notice of Compliance to Boehringer Ingelheim (Canada) Ltd. for the drug product Aptivus.

Aptivus contains the medicinal ingredient tipranavir which is a non-peptidic protease inhibitor.

Aptivus co-administered with low dose ritonavir, is indicated for combination antiretroviral treatment of HIV-1 infected adult patients with evidence of viral replication, who are treatment-experienced and have HIV-1 strains resistant to multiple protease inhibitors. HIV-1 encodes an aspartyl protease that is essential for the cleavage and maturation of viral protein precursors. Tipranavir is a non-peptidic inhibitor of the HIV-1 protease that inhibits viral replication by preventing the maturation of viral particles.

The drug submission for Aptivus was reviewed under the Priority Review Policy. Aptivus, co-administered with ritonavir in antiretroviral-experienced patients, demonstrated a significant increase in efficacy with an improved benefit/risk profile compared to existing therapies for HIV, a condition that is not adequately managed by a drug marketed in Canada.

The market authorization was based on quality, preclinical, and clinical information. The clinical data (N=1159) was derived from analyses of 24-week data from two pivotal ongoing studies measuring effects on plasma HIV-1 RNA levels and CD4 cell counts. The data submitted demonstrate that Aptivus can be administered safely when used under the conditions stated in the Product Monograph.

Aptivus (250 mg tipranavir) is presented in capsule form. The recommended dose of Aptivus capsules is 500 mg co-administered with 200 mg ritonavir (low-dose ritonavir), twice daily. Dosing guidelines are available in the Product Monograph.

Aptivus is contraindicated in patients with known hypersensitivity to the active substance or to any of the ingredients of the product. Patients with moderate or severe (Child-Pugh Class B or C respectively) hepatic insufficiency are also contraindicated. Co-administration of Aptivus with low-dose ritonavir, along with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated. Detailed conditions for the use of Aptivus 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 Aptivus co-administered with low dose ritonavir is favourable for combination antiretroviral treatment of HIV-1 infected adult patients with evidence of viral replication, who are treatment-experienced and have HIV-1 strains resistant to multiple protease inhibitors.

3 SCIENTIFIC AND REGULATORY BASIS FOR DECISION

3.1 Quality Basis for Decision

3.1.1 Drug Substance (Medicinal Ingredient)

Manufacturing Process and Process Controls

Materials used in the manufacture of the drug substance, tipranavir, are considered to be suitable and/or meet standards appropriate for their intended use. The manufacturing process is stereospecific and yields predominantly the single desired isomer.

Specifications for the starting materials and isolated intermediates are considered to be acceptable.

The manufacturing process is considered to be adequately controlled within justified limits.

Characterisation

Tipranavir has been well characterized. The tipranavir molecule contains two chiral centers although it is synthesized as a single isomer. Representative spectra have been provided.

Impurities and degradation products arising from manufacturing and/or storage were reported and characterized. The pathways leading to each potential impurity were fully discussed. The proposed limits were considered satisfactorily qualified (e.g., within recommended ICH limits, toxicological studies). Control of the impurities in the drug substance is therefore considered to be acceptable.

Control of Drug Substance

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

The specifications are considered acceptable for the drug substance. Results from batch analysis were within the proposed acceptance criteria.

The proposed container/closure system is also considered to be acceptable.

Stability

Based on the properties of tipranavir and the long-term and accelerated stability data, the proposed re-test period, storage, and shipping conditions are considered to be satisfactory for the drug substance.

3.1.2 Drug Product

Description and Composition

Tipranavir is formulated as a Self-Emulsifying Drug Delivery System (SEDDS) which is filled in soft gelatine capsules. Aptivus (tipranavir 250 mg) capsules are pink, oblong, soft gelatin capsules imprinted in black with "TPV 250". They are packaged in high-density polyethylene (HDPE) bottles with a child-resistant closure containing 120 capsules.

Each Aptivus capsule contains 250 mg of tipranavir. Non-medicinal ingredients include Cremophor® EL, ethanol, mono/diglycerides of caprylic/capric acid, propyl gallate, propylene glycol, purified water, and trometamol.

The capsule shell contains gelatin, iron oxide red, propylene glycol, purified water, 'sorbitol special glycerin blend' (d-sorbitol, 1,4-sorbitan, mannitol and glycerin) and titanium dioxide.

The black printing ink contains ammonium hydroxide, ethyl acetate, iron oxide black, isopropyl alcohol, Macrogol, polyvinyl acetate phthalate, propylene glycol, purified water and SDA 35 alcohol.

The excipients are USP/NF standard except for the mono/diglycerides of caprylic/capric acid and the capsule shell and imprinting ink. Specifications for non-compendial excipients have been provided as appropriate and are considered to be acceptable. Cremephor® EL has been reported to increase patient toxicity and can lead to hypersensitivity reactions. The appropriate clinical division in Health Canada was consulted with respect to the toxicology data used to assess the safety of this excipient.

The excipients used in the self-emulsifying drug delivery systems (SEDDS) formulation are common to SEDDS and the choice is considered to be acceptable. The SEDDS is composed of mixtures of oils and surfactants, ideally isotropic, and sometimes containing co-solvents, which emulsify spontaneously to produce fine oil-in-water emulsions when introduced into aqueous phase under gentle agitation.

Pharmaceutical Development

The description of the formulation development is acceptable. Changes to the manufacturing process and formulation made throughout the development are also considered acceptable. The Phase I, II, and III studies were conducted using the same formulation as proposed for marketing in Canada.

Manufacturing Process and Process Controls

A standard process, utilizing well-established manufacturing technology, is used in producing the solution-filled soft gelatin capsules. The commercial manufacturing process of Aptivus includes three major operations: manufacture of bulk fill solution, manufacture of the gel mass, and manufacture of the finished capsules. The flow diagram and narrative description of the manufacturing process are considered to be acceptable. The process is considered adequately controlled within justified limits.

Control of Drug Product

Aptivus is tested to verify that its identity, purity, appearance, dissolution, content uniformity, and levels of degradation products and microbial impurities are within acceptance criteria.

The method descriptions, in-process controls, and validation data are considered to be acceptable. Data from batch analyses were within the proposed specification limits.

The proposed limits for degradation products were considered satisfactorily qualified (e.g., within recommended ICH limits, toxicological studies).

Stability

Based upon the long-term and accelerated stability study data submitted, the proposed 36-month shelf life for Aptivus capsules packaged in HDPE bottles and stored under refrigeration (2-8°C) is acceptable. Once opened, the bottle can be stored for up to 60 days at 25°C with excursions permitted at 15-30°C.

Stability samples were within specification limits at all times up to 36 months when stored under the ICH refrigeration storage conditions of 5°C±3°C/NR RH. Samples stored under ICH accelerated conditions of 25°C/60% RH were also within the proposed specification limits up to 6 months. No trends or failures were observed in the data. Results also demonstrated that excursions from controlled room temperature storage will not adversely affect the quality of the drug product.

3.1.3 Facilities and Equipment

The design, operations and controls of the facility and equipment that are involved in the production are considered suitable for the products manufactured at the site.

3.1.4 Adventitious Agents Safety Evaluation

The gelatin in the capsule shell is of animal origin. A letter of attestation confirming that the material is not from a BSE/TSE-affected country/area has been provided for this product indicating that it is considered to be safe for human use.

3.1.5 Summary and Conclusion

This New Drug Submission is considered to meet the requirements of Division C.08.002 of the *Food and Drug Regulations* insofar as the Quality (Chemistry and Manufacturing) information is concerned. The Chemistry and Manufacturing information submitted for Aptivus has demonstrated that the drug substance and drug product can be consistently manufactured to meet the specifications agreed upon. 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

Initial examination showed tipranavir to be a more potent antiviral agent in contrast to other antiviral agents in early development. Results showed that the ability of HIV variants to grow at increasing concentrations of tipranavir required the sequential accumulation of mutations in the viral protease gene. Decreased susceptibility to tipranavir was initially seen in mutations L33F and I84V, followed by K45I, I13V, V32I, V82L, M36I, A71V, L10F and I54T/V. Up to 10 mutations were observed in the protease gene of viruses growing in the presence of 20µM of tipranavir and showing an 87-fold decrease in susceptibility to the inhibitor. In addition, a mutation in the CA/P2 p55 gag cleavage site and a mutation in the transframe region were observed in resistant viruses. The only single mutation identified that showed reduced susceptibility to tipranavir was L33F. Viruses containing the combinations L33F/I84V and L33I/I84V showed 3.3 and 1.8 fold resistance, respectively. In a phenotypic analysis of 141 HIV clinical isolates from patients showing post-treatment decreased susceptibility to other protease inhibitors, 65% of the isolates remained susceptible to tipranavir.

In vitro tests showed that the antiviral activity of tipranavir was reduced (2- to 7-fold) as a result of protein binding (human serum albumin, human plasma, a1-acid glycoprotein). Tipranavir protein binding was very high in all animal models and in humans. The effect was concentration-dependent with higher levels of protein in the assay resulting in larger decreases in antiviral activity.

Tipranavir showed a synergistic effect with zidovudine, delavirdine, and ritonavir, and an additive effect with amprenavir and lopinavir. No significant antagonism was observed with the combinations studied.

Tipranavir did not appear to display binding affinity for any site except the CCK-A receptor at the highest concentration; however this was not fully explored.

The effects of tipranavir on various cardiac parameters were examined. Studies indicated that tipranavir has a low proarrhythmic potential. Tipranavir had no effect on action potential parameters, however, changes in mean arterial pressure were noted as were changes in heart rate, respiratory rate, PR interval and ST segment division. The sponsor stated that they did not consider these changes toxicologically relevant, however it is felt that these cardiac effects should be further investigated in the pre-clinical toxicity studies and clinical studies. Noted changes in rats that are most likely to be observed in human studies include changes in gastric secretion, gastric emptying and gastrointestinal propulsion.

3.2.2 Pharmacokinetics

Absorption

Initial formulations of tipranavir appeared to have very low oral bioavailability in all species. The development of the free acid self-emulsifying drug delivery system (SEDDS) formulation and the co-administration of ritonavir increased the bioavailability of tipranavir substantially.

Fasting and the intake of food had no apparent effect on tipranavir absorption. In rats and mice, females seemed to have significantly increased bioavailability, higher plasma concentrations, higher drug exposure (AUC values), and lower clearance of tipranavir. The gender effect appeared to apply to other animal models as well, but was not as apparent.

Distribution

Tipranavir was highly bound to human plasma (99.97%) and appeared to be concentration-dependent. There was very little penetration into the brain tissue and cerebral spinal fluid.

Tipranavir was equally distributed in blood and plasma with the greatest concentration in the liver (approximately 50-fold higher than in whole blood) followed by the lung, blood, adrenal gland, intestine and kidney. Maximum drug levels occurred approximately 4 hours after dosing.

Metabolism

Tipranavir was shown to be metabolized by the liver and when administered orally it underwent substantial first pass metabolism. No major metabolites of tipranavir were identified. Metabolites that were identified included glucoronide conjugates of tipranavir, dehydrogenation metabolites, tricyclic regioisomers and phenylhydroxymethyl structures. Metabolism occurred via the cytochrome P450 (CYP) system in the liver and CYP3A4 was identified as the enzyme most likely to be involved in the metabolism. Male and female rats that were treated with high doses of tipranavir showed significant dose-related increases in liver weight, CYP specific content, and CYP2B and CYP3A enzymatic activity. In male rats, a significant dose-related decrease in CYP2C11 enzyme activity was noted. Dogs treated with high doses showed increased CYP3A12 and CYP2B11 activity. These results suggest the occurrence of enzyme induction, and the liver as the primary organ of toxicity.

Excretion

Tipranavir was primarily excreted in the faeces. Biliary excretion was the primary route of elimination in all test species, with the majority of tipranavir being recovered in the faeces and secondly in the urine.

3.2.3 Toxicology

Single-Dose Toxicity

In the single-dose toxicity studies of tipranavir in mice, the maximum non-lethal dose was 2000 mg/kg/day and the minimum lethal dose was 3000 mg/kg/day. In rats, it was found that divided doses of 1500 to 3000 mg/kg/day were acutely lethal. In both species, the drug-related clinical signs were similar and generally gastrointestinal. Clinical signs included salivation, soft stool, inactivity, wet and stained anogenital/muzzle haircoat, ptosis, laboured breathing, unsteady gait, seizures, no feces, prone position, moribund appearance and body weight loss. In the rat at doses of 1500 and 3000 mg/kg/day, there was also a slight prolongation of activated partial thromboplastin and prothrombin times and discoloration of the small and large intestines. Generally, female animals tended to show signs of toxicity at lower drug levels than males. The reason for this is likely due to the higher overall plasma concentrations in females at equivalent doses to males, as demonstrated in the repeat-dose toxicity studies.

Repeat-Dose Toxicity

Repeat-dose toxicity studies demonstrated NOAEL (the highest level at which no adverse effect is observed) values of approximately 40 mg/kg/day and 300 mg/kg/day for rats and dogs, respectively. Repeated dermal applications resulted in sufficient exposure to induce systemic toxicity (primarily hepatotoxicity) at a minimal toxic dermal dose level of 12 mg/day for 28 days.

Clinical signs that increased in frequency and severity with increased doses in all the repeat-dose toxicity studies included salivation, decreases in food consumption and body weight gain, staining of the anogenital region, decreased motor activity, emesis, soft stool/diarrhoea, dyspnoea, ptosis, changes in haircoat, and distended abdomens. Additionally, excessive bleeding after retro-orbital bleeding procedures in rats was noted in Study U04-3111 due to changes in coagulation factors. In several studies, deaths resulting from iatrogenic effects were noted. A gender effect was noted with an increased observation of adverse effects in females.

The liver was the primary organ of toxicity with hepatotoxicity noted in all animal models. Changes to the liver included increases in liver weight, discoloration at necropsy, prominent lobular architecture, hepatocellular hypertrophy and hydropic liver change, hepatocellular midzonal necrosis and increased mitotic index, cholangiohepatitis, Kupffer cell hyperplasia, and interstitial fibrosis. Hepatotoxicity was believed to be a result of the effects of tipranavir on the cytochrome P450 system and enzyme induction. Many hepatotoxic effects were reversible after discontinuation of tipranavir.

The thyroid was generally considered the secondary organ of toxicity with effects such as minimal to mild follicular cell hypertrophy of the thyroid, decreases in tri-iodothyronine and thyroxine concentrations, and increases in thyroid stimulating hormone. The sponsor notes that "thyroid follicular hypertrophy in rats is a secondary effect due to hepatic enzyme induction caused by tipranavir, as the primary clearance of thyroid hormone in rodents is via glucuronidation and biliary excretion". As a result, it is possible that this effect may not be observed in humans.

In most dose groups of the various animal models tested, studies showed dose-related decreases in prothrombin and activated partial thromboplastin times, and treatment-related increases in fibrinogen. Decreases in red blood cell parameters, white blood cell counts and absolute lymphocyte counts were also reported.

In Study U00-3089, an electrocardiogram analysis was performed and showed notable changes in heart rate, PR interval and QRS interval in beagle dogs of each dose group (30, 75, 160, and 320 mg/kg/day).

Changes in clinical chemistry included elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total protein in mice. In rats, results showed decreases in mean cholesterol and potassium, alkaline phosphatase activity and potassium; and increases in total protein, albumin and globulin, serum calcium, cholesterol, and blood urea nitrogen. Increased levels of serum alkaline phosphatase levels, and decreases in albumin, total protein and albumin/globulin ratios and calcium levels were seen with mid to high doses in dogs.

Genotoxicity

Tipranavir shows no genotoxic/mutagenic potential. The sponsor has fulfilled all of the ICH recommendations regarding the genotoxicity studies, and no evidence of genotoxicity was shown.

Carcinogenicity

The carcinogenicity studies have not yet been submitted. The Product Monograph contains a statement to the effect that carcinogenicity studies are currently ongoing and that there is currently no data available on tipranavir's potential to induce carcinogenesis.

Reproductive and Developmental Toxicity

Reproductive and developmental toxicity due to tipranavir administration cannot be discounted due to the occurrence of the following adverse effects. Studies with rats showed decreased fetal body weight and incidence of unossified sternebrae at 400 and 1000 mg/kg/day. Rabbit studies showed maternal toxicity including liver toxicity, weight loss, decreased weight gain and scant/soft feces at the 350 and 750 mg/kg/day doses. Embryo toxicity was observed and included increased post-implantation loss, and decreased mean live fetus weight. Results also showed postnatal reductions in body weight, body weight gain and food consumption in the dams and reductions in pup growth throughout lactation. The Product Monograph provides the results of the fetal toxicity tests with reference to human exposure.

3.2.4 Summary and Conclusion

Tipranavir is a non-peptidic inhibitor of HIV-1 protease. Tipranavir is very highly protein-bound in human plasma and is noted for its relatively high genetic barrier to resistance. Tipranavir is primarily metabolized via the cytochrome P450 system in the liver with CYP3A4 identified as the enzyme most likely involved in the metabolism.

The major areas of toxicity identified in the acute and chronic toxicity studies include prolongation of activated partial thromboplastin and prothrombin times, liver effects, thyroid effects, and gastrointestinal effects. The liver was the primary organ of toxicity and exhibited changes including increases in weight and hepatocellular hypertrophy among others, at a wide range of exposures. The majority of these effects were reversible upon discontinuation of tipranavir. Changes in cardiac parameters such as heart rate, PR interval and QRS interval were noted and were further examined in the clinical studies.

Carcinogenicity studies have not yet been completed for tipranavir. Tipranavir showed no significant evidence of genotoxicity, or reproductive and developmental toxicity.

Overall, the non-clinical pharmacology and toxicology studies support the use of tipranavir for the proposed indication.

3.3 Clinical Basis for Decision

3.3.1 Pharmacodynamics

The pharmacodynamics of the medicinal ingredient of Aptivus (tipranavir) were studied in a randomized, open-label, parallel group design in 31 treatment-naive HIV-1 infected patients with three different 14-day treatment regimens. Tipranavir (TPV) was administered in a self-emulsifying drug delivery system (SEDDS), either alone at a dose of 1200 mg twice a day (BID), or at 300 mg or 1200 mg BID administered with ritonavir (RTV) 200 mg BID.

After two weeks of treatment, median HIV-1 RNA levels were decreased by 0.77, 1.43, and 1.64 $\log_{10}$ copies/mL in the TPV 1200 mg, TPV 300 mg + RTV, and TPV 1200 mg + RTV groups, respectively. The greater decrease in viral levels in the ritonavir-boosted TPV groups compared to the TPV 1200 mg group was statistically significant, however the differences between the two RTV groups were not. Nine subjects (82%) in the TPV 1200 mg + RTV group had a 1.5 $\log_{10}$ or greater decrease in HIV-1 RNA by Day 15. Four subjects (40%) in the TPV 300 mg + RTV group had a similar decrease, while no subjects in the TPV 1200 mg group achieved a 1.5 $\log_{10}$ decrease.

Median first order viral elimination rates were estimated to be -0.06, -0.13, and -0.14 for the TPV 1200 mg, TPV 300 mg + RTV, and the TPV 1200 mg + RTV groups, respectively.

By the end of the study, the immune competence, measured by median CD4 cell counts, had increased by 42, 75 and 83 cells/mm^3 in the TPV 1200 mg, TPV 300 mg + RTV, and TPV 1200 mg + RTV groups, respectively; however, the difference between groups was not statistically significant.

Co-administration of tipranavir and ritonavir resulted in substantial increases in tipranavir exposure and concentration, compared to tipranavir alone. In addition, tipranavir oral clearance was decreased and the apparent elimination half-life was increased when tipranavir was coadministered with ritonavir.

3.3.2 Pharmacokinetics

Absorption

Tipranavir pharmacokinetics appear to be linear for single doses up to 200 mg, however there appears to be some non-linearity upon multiple dosing.

Two studies examined the effects of ritonavir on the steady state pharmacokinetics of tipranavir. Results showed a large increase in tipranavir systemic drug exposure; the increases in C_{max} (four-fold) and AUC (5- to 13-fold) were thought to be due to the inhibition of CYP3A4 by ritonavir. Tipranavir appeared to significantly induce the metabolism of ritonavir, with a 5-fold reduction in ritonavir's average steady-state concentrations.

Distribution

In circulation, tipranavir was extensively bound to plasma proteins. The binding of tipranavir in normal subjects was not significantly different from the extent of binding in HIV-positive subjects. The influences of additional highly-bound drugs on the free fraction of tipranavir were investigated. In the presence of delavirdine, at its therapeutic C_{max}, the unbound fraction of tipranavir increased by approximately 2-fold. Warfarin also caused an increase in the unbound fraction of tipranavir, but to a lesser extent. Saquinavir, indinavir, trimethoprim, and sulfamethoxazole had no effect on the binding of tipranavir to plasma proteins. The effect of tipranavir on the binding of other drugs was not investigated.

Metabolism

Tipranavir appears to induce its own metabolism (autoinduction). *In vitro* metabolism studies with human liver microsomes indicated that CYP3A4 is the predominant CYP isoform involved in tipranavir metabolism.

The metabolism of tipranavir in the presence of low-dose ritonavir is minimal. Only a few metabolites were found in plasma, and all were at trace levels (0.2% or less of the plasma radioactivity).

Excretion

Administration of ^{14}C-tipranavir to subjects that received tipranavir/ritonavir 500 mg/200 mg BID demonstrated that the main route of excretion of ^{14}C-tipranavir-derived radioactivity was via the faeces with greater than 80% of the total radioactivity recovered in the faeces. Excretion in the urine was the minor route of elimination with less than 5% of the total radioactivity recovered in the urine.

Special Populations

A small pharmacokinetic study was carried out in patients with mild (n = 9) and moderate (n = 3) hepatic impairment along with age- and sex-matched controls. While there were no statistically significant differences, the study had very low statistical power making it difficult to make any definitive conclusions. The Product Monograph was modified to reflect this fact.

Drug Interaction Studies

Drug interactions were extensively studied covering the nucleoside reverse transcriptase inhibitors (abacavir, didanosine, lamivudine, stavudine, tenofovir and zidovudine); non-nucleoside reverse transcriptase inhibitors (efavirenz and nevirapine); protease inhibitors (amprenavir, lopinavir, ritonavir and saquinavir) and other drugs (atorvastatin, clarithromycin, fluconazole, loperamide, Maalox, norethindrone-ethinyl estradiol and rifabutin). Of the three classes of antiretrovirals tested, the protease inhibitors were the most significantly affected by tipranavir coadministration with substantial reductions in all the protease inhibitors tested. Of note, there was a high dropout rate with the combination of nevirapine and tipranavir, with and without ritonavir, because of poor tolerability in the healthy volunteers. Tipranavir/ritonavir significantly increased the exposure of atorvastatin which would increase the risk of atorvastatin's side effects (e.g. myopathy), such that the combination is not recommended. In addition to a significant reduction in ethinyl estradiol concentrations, there was poor tolerability in the healthy volunteers (rash and arthralgias) with this combination. The only other major interaction was with rifabutin; levels of rifabutin were dramatically increased. Precautionary measures would include the dramatic reduction of the rifabutin dosage (150 mg two or three times weekly).

3.3.3 Clinical Efficacy

The submission contained two pivotal Phase III studies, and two supporting studies. The pivotal studies, studies 1182.12 and 1182.48, will hereafter be referred to by their acronyms, the RESIST-1 and RESIST-2 studies.

Pivotal Studies

The RESIST-1 and RESIST-2 studies provided efficacy data from the 24-week mark, but are being continued in order to provide 48-week data. The RESIST-1 study had 620 patients, and the RESIST-2 study had 863 patients, although only 539 received 24 weeks of treatment. Both of these studies had adequate population sizes.

The RESIST-1 and RESIST-2 studies were randomized, open-label, multicentre studies in HIV-positive, triple-class experienced patients, evaluating treatment with tipranavir, coadministered with low-dose ritonavir, plus an optimized background drug regimen (OBR) that was individually defined for each patient based on genotypic resistance testing and patient history. The comparator regimen included a ritonavir-boosted protease inhibitor (PI, also individually defined) plus an OBR. All patients had received at least two PI-based antiretroviral regimens and were failing a PI-based regimen at the time of study entry. At least one primary protease gene mutation from among 30N, 46I, 46L, 48V, 50V, 82A, 82F, 82L, 82T, 84V or 90M had to be present at baseline, with not more than two mutations on codons 33, 82, 84 or 90. The 1159 patients included in the primary interim analysis had a median age of 43.0 years (range 17-80), were 88% male, 73% white, 14 % black and 1% Asian.

In the tipranavir and comparator arms, the median baseline CD4 cell counts were 155 and 158 cells/mm^3, respectively, (ranges 1-1893 and 1-1184 cells/mm^3); and the median baseline plasma HIV-1 RNA were 4.83 and 4.82 $\log_{10}$ copies/mL, respectively (ranges 2.34-6.52 and 2.01-6.76 $\log_{10}$ copies/mL).

The primary efficacy endpoint was the proportion of patients with a treatment response ($\geq$1 $\log_{10}$ reduction in 2 consecutive viral load measurements without evidence of treatment failure) at 48 weeks. Given that this submission provided only 24-week data, only secondary efficacy endpoints were used.

The secondary endpoints included determinations of:

- Proportion of patients with a treatment response ($\geq$1 $\log_{10}$ reduction in 2 consecutive viral load measurements without evidence of treatment failure) at 24 weeks

- Virologic response based on the proportion of patients with $\geq$1 $\log_{10}$ reduction in viral load from baseline
- Virologic response based on the proportion of patients with a viral load <400 copies/mL
- Virologic response based on the proportion of patients with a viral load <50 copies/mL
- Change from baseline in viral load at each study visit to week 24
- Daily average change from baseline in viral load to week 24
- Change from baseline in CD4 count at each study visit to week 24
- Proportion of patients with treatment-emergent AIDS-defining illnesses reported in the first 24 weeks of treatment
- Trough PI plasma levels.

Results from RESIST-1 showed that there were approximately 100 fewer patients who completed 24 weeks on the comparator arm than in the tipranavir arm primarily due to treatment failure. This is significant, given that approximately 300 were treated originally in each arm. After 8 weeks, 15 patients (4.9%) in the comparator arm discontinued for lack of initial virologic response or virologic failure, compared to only one patient (0.3%) in the tipranavir arm. However, 15 tipranavir patients (4.8%) were discontinued due to adverse events compared to only 7 (2.3%) in the comparator arm. By week 24, 106 patients prematurely discontinued in the comparator arm, compared to only 23 patients in the tipranavir arm.

Based on the analyses of treatment response, there was a significant difference ($p<0.0001$) between the two treatment arms. Therefore, tipranavir can be considered superior to the comparator arm. Consequently, the tipranavir/ritonavir combination can be viewed as superior to lopinavir/ritonavir, amprenavir/ritonavir, and saquinavir/ritonavir combinations for this patient population. No determination of superiority could be established for indinavir due to the lack of patients using that particular comparator regimen.

The fact that there were nearly 70% of comparator arm patients who failed to achieve a confirmed 1 $\log_{10}$ reduction in viral load, compared to only 45% in the tipranavir arm also shows the superiority of tipranavir to the comparator protease inhibitors under the conditions of this clinical trial. As well, the lack of treatment response due to a change in medication or discontinuation because of virologic failure occurred more frequently in the comparator arm (35.3%) than in the tipranavir arm (4.2%).

In the tipranavir arm, a greater treatment response was evident very early on, achieving 53.1% compared to only 34.3% in the comparator arm as early as week 2, with the differences persisting through week 24. As of week 24, 43.4% of the patients in the tipranavir arm had achieved a reduction of >1 $\log_{10}$ in viral load, compared to only 23.3% in the comparator arm,

which was significantly different ($p<0.0001$). Similarly, 25.1% of the patients in the tipranavir arm had achieved a viral load <50 copies/mL, compared to only 10.0% in the comparator arm, which was significantly different ($p<0.001$). For patients who were treatment experienced, it was noted that the treatment response for patients in the tipranavir arm did not differ drastically if there were fewer than 12, or more than 19, protease gene mutations.

The median increase from baseline in CD4 count was higher in the tipranavir arm (36 cells/mm^3) than in the comparator arm (6 cells/mm^3). Coadministration with enfuvirtide significantly increased (a) the proportion of treatment responders, (b) the median reduction in log_{10} copies/mL plasma HIV-1 RNA levels, and (c) the median CD4 count from baseline, in the tipranavir arm as compared to the comparator arm.

Results from RESIST-2 showed superior efficacy of tipranavir/ritonavir (TPV/RTV) based on significant changes in established and validated surrogate markers for HIV-1 disease (plasma HIV-1 RNA) and immune competence (CD4 cell count) after 24 weeks of treatment.

A significantly higher proportion ($p<0.0001$) of patients on TPV/RTV (41%) achieved a treatment response at week 24 vs. patients in the comparator arm (15%). In the sensitivity analysis after 24 weeks, with 44.4% of the tipranavir patients achieving a treatment response compared to only 18.6% in the comparator arm, it is concluded that tipranavir is significantly superior to the comparator protease inhibitors ($p<0.0001$), with the exception of indinavir.

The proportion of patients with virologic response after 16 weeks was significantly higher in the tipranavir arm (46%) than in the comparator arm (21%). Similar results were noted after 24 weeks.

The median log_{10} reduction from baseline in viral load was consistently higher in the tipranavir arm (-0.72) than in the comparator arm (-0.22) after 24 weeks of treatment. When combined with enfurtivide, tipranavir increases its reduction in the median viral load notably (to -2.06 log_{10}), while the same cannot be said about the comparator arm (-0.07 log_{10}). The median daily average change from baseline in viral load up to 24 weeks was -1.01 log_{10} in the tipranavir arm versus -0.25 log_{10} in the comparator arm.

A higher proportion of patients receiving TPV/RTV (33.2%) achieved plasma HIV-1 RNA levels <400 copies/mL compared with CPI/RTV (12.7%). A similar difference was observed between the proportions of patients with plasma HIV-1 RNA levels <50 copies/mL (TPV/RTV 22.1% and CPI/RTV 8.6%).

At week 24, an increase in the CD4 cell count of 31 cells/mm^3 was noted in the tipranavir arm, compared to an increase in the CD4 cell count of 1 cell/mm^3 in the comparator arm. When enfurtivide was added, the cell counts became 72 and -1 cells/mm^3, respectively.

As the baseline fold in IC50 increases, the log_{10} change from baseline in viral load, treatment response and virologic response all decline at week 24. This shows an interaction between the phenotypic resistance to tipranavir and the effect of the drug.

RESIST-1 and RESIST-2 demonstrated that tipranavir is superior to the comparator treatment regimens, with the exception of the indinivar/ritonavir combination, and that was due to a lack of patients using that particular comparator regimen.

In summary, the results of both pivotal studies show that the TPV/RTV regimen (in combination with other antiretrovirals) was significantly more effective than the genotypically-defined CPI/RTV-based regimen (in combination with other antiretroviral agents) in achieving a treatment response in patients who had previously received multiple antiretroviral drugs and had multi-drug resistant HIV. The benefits provided by a TPV/RTV-based regimen through 24 weeks were enhanced in terms of proportion of treatment responders and duration of response by coadministration of other active antiretroviral agents, including enfuvirtide.

Supporting Studies

In one of the supporting studies that examined multiple protease inhibitor (PI) experienced subjects failing on their current PI regimen, substitution of tipranavir/ritonavir at doses of 500 mg/100 mg or 1000 mg/100 mg both resulted in a greater than 2 log_{10} reduction in viral load which was sustained beyond 48 weeks. In another supporting study, conducted in single-PI experienced subjects, tipranavir/ritonavir at doses of 500 mg/100 mg and 1250 mg/100 mg yielded a maximum of 1.8 log_{10} reduction in HIV-1 RNA levels, which did not differ significantly from the ritonavir-boosted saquinavir control group (400 mg/400 mg). By 48 weeks, however, the efficacy in all treatment groups had declined substantially.

Tipranavir treatment has been shown to select for L10V, I84V, I54V, L33F and L33I resistance mutations, and select against the V82A mutation. The H69Y, T74A, and V82L mutations were also selected for, but the significance of these mutations is uncertain.

Increased phenotypic resistance to PIs in general, including tipranavir, occurred following treatment with tipranavir/ritonavir at a dose of 500/100 mg, but not with the 1250/100 mg dose.

Microbiology Studies

A microbiology report was based on resistance data from seven clinical trials in HIV-positive adults: three Phase II dose ranging studies, two Phase III controlled trials, one Phase IIb pharmacokinetic and safety trial of dual-boosted PI use, and one long-term Phase III rollover safety trial.

Sixteen protease mutations were associated with tipranavir and comprised the tipranavir mutation score as follows: 10V, 13V, 20M/R/V, 33F, 35G, 36I, 43T, 46L, 47V, 54A/M/V, 58E, 69K, 74P, 82L/T, 83D and 84V. The mutation 82L was not previously associated with any protease inhibitors. The sponsor also noted that the multi-PI resistant mutations L90M and V32I were not associated with tipranavir resistance. Mutations D30N, I50V, and N88D were associated with increased tipranavir susceptibility. Saquinavir appeared to be the only protease inhibitor that maintained antiviral activity against isolates with increased tipranavir resistance. The most common emerging mutations associated with decreased tipranavir susceptibility were mutations L33F, V82L/T and I84V with mutations L33F and I84V occurring first. Antiviral response as compared to baseline genotype and phenotype was generally positive though the response decreased with increasing number of mutations. Results have demonstrated that tipranavir poses a high genetic barrier to resistance development and with the appropriate background regimen, viral load reduction in patients with extensive viral mutations appears possible.

3.3.4 Clinical Safety

An examination of the safety results from the two pivotal trials (RESIST-1 and RESIST-2), and other supporting studies as well as safety data published in peer-reviewed journals or as conference abstracts, indicate that tipranavir is tolerated as well as other protease inhibitors in highly treatment-experienced patients.

Pivotal Studies

The study design of the two pivotal studies, RESIST-1 and RESIST-2, is described in section *3.3.3 Clinical Efficacy*.

The safety endpoints for the two pivotal studies included:

- Proportion of patients with treatment-emergent adverse events
- Proportion of patients with serious adverse events
- Proportion of patients reporting adverse events by severity
- Proportion of patients with laboratory test abnormalities

- Laboratory test changes over time
- Discontinuations due to adverse events

Common adverse events included diarrhea, nausea, vomiting, pyrexia, fatigue, increased ALT and AST, rash, and hypertriglyceridaemia.

In RESIST-1, there were more serious adverse events in the tipranavir arm as well as more intense serious adverse events that were related to the study drug. The percentage of patients who discontinued the study drug due to serious adverse events was greater in the tipranavir arm than the comparator arm (4.2% vs 1.0%). In the tipranavir arm, diarrhea, nausea, increased AST, abdominal pain, increased ALT, hyperlipidemina, hypertriglyceridemia and vomiting occurred as severe drug-related adverse events, while diarrhea and fatigue occurred as severe drug-related adverse events in the comparator arm. In the tipranavir arm, elevated liver enzymes were disproportionately more frequent among drug-related serious adverse events than among all serious adverse events. More patients in the tipranavir arm had significant ALT and AST elevations than the comparator arm (3.5% vs. 0.6%). Also, the AST elevations occurred more frequently in the tipranavir group over time, suggesting a potential long-term hepatic effect of tipranavir. The results suggest that hepatotoxicity may be an issue for tipranavir. While there was no evidence of hepatitis occurring in this study, fatal cases of hepatitis did occur in the long-term rollover study, so the effects of tipranavir on the liver cannot be understated. Tipranavir is to be contraindicated in moderately and severely hepatically impaired patients (Childs-Pugh B or C), and it should be used with caution in mildly hepatically impaired patients.

In RESIST-2, diarrhea, nausea, elevated liver enzymes, headache, rash and hyperlipidemia were more prevalent in the tipranavir arm, compared to the comparator arm, which was consistent with the known effects of the product. Adverse events considered related to study medication differed between the treatment arms, with frequencies of 40.5% in the tipranavir arm and 22.2% in the comparator arm. In the tipranavir arm, the most frequent adverse events were diarrhea (22.5%), nausea (13.6%), headache (9.7%), pyrexia (9.2%) and vomiting (6.9%), whereas in the comparator arm, the most frequent adverse events were diarrhea (18.5%), nausea (7.5%), pyrexia (7%), vomiting (6.5%) and headache (6.1%). The vast majority of the drug-related severe adverse reactions were associated with liver toxicity, including an increase in the liver enzymes (AST, ALT, GGT), the transaminases or cytolytic hepatitis, liver disorder, hepatitis steatosis, or toxic hepatitis. The most frequent adverse events leading to study drug discontinuation were gastrointestinal disorders followed by hepatobiliary disorders, including cytolytic hepatitis, and toxic hepatitis. Also, the addition of hyperamylasemia and peripheral neuropathy suggest that there may also be an effect on the pancreas, and slight mitochondrial toxicity.

In summary, the adverse event profiles of the 2 treatment groups in both pivotal studies, RESIST-1 and RESIST-2, were consistent with the usual manifestations of advanced HIV-infection and the common side effects of antiretroviral therapy in treatment-experienced patients. The frequencies of clinical adverse events and common laboratory test abnormalities were consistent with those in similar clinical trials. The safety profiles exhibited some consistent differences, with the tipranavir arm showing higher frequencies most importantly for total adverse events, severe adverse events, serious adverse events, adverse events leading to discontinuations from study medication, ALT elevations and triglyceride elevations. Mortality, whether calculated as crude numbers or as numbers adjusted for exposure, was similar between the tipranavir and comparator arms.

Supporting Studies

In support of this application, a number of Phase I and Phase II clinical studies were reviewed.

The clinical study of tipranavir on QT prolongation did not meet current ICH standards, therefore, the effect of tipranavir on QT prolongation is unclear. The sponsor has agreed to include in the Product Monograph a precaution stating that the effect of tipranavir on QT prolongation has not been thoroughly characterized in the clinical studies. The sponsor is conducting a thorough clinical QT study, a Phase IV commitment to the U.S. Food and Drug Administration at the time of approval.

The most common adverse events observed included nausea, diarrhea, vomiting, fatigue and rash. The incidence of gastrointestinal side effects, in particular, was related to the tipranavir dose. In one study, the incidence of rash in the combined tipranavir/ritonavir 500/100 mg and 1250/100 mg groups exceeded that seen in the saquinavir control group by more than 10%.

Severe adverse events were seen in approximately 40-50% of tipranavir-treated subjects, increasing with dose. The most commonly observed severe adverse events were nausea, vomiting, increased ALT, increased GGT, and hypertriglyceridemia. Decreased white blood cell counts were also commonly seen.

3.4 Benefit/Risk Assessment and Recommendation

3.4.1 Benefit/Risk Assessment

The drug submission for Aptivus was granted Priority Review because Aptivus, coadministered with ritonavir in antiretroviral-experienced patients, demonstrated a significant increase in efficacy with an improved benefit/risk profile compared to existing therapies for HIV, for a condition that is not adequately managed by a drug marketed in Canada.

In the two submitted pivotal studies, the medicinal ingredient of Aptivus (tipranavir) demonstrated efficacy in patients who have a very limited selection of alternate medications. Overall, there was a significant difference in terms of treatment response between the tipranavir arm and the comparator arm. There was also a large difference between both arms in terms of numbers of discontinuations due to lack of initial virologic response or virologic failure.

Coadministration of tipranavir with enfurtivide was found to enhance response rates, particularly as the number of baseline primary protease gene mutations increased. Tipranavir can make a very good addition, based on its efficacy in highly treatment-experienced patients, to the list of antiretrovirals used as potential salvage therapy.

While there is a significant benefit for tipranavir for patients with HIV-1 strains resistant to most other protease inhibitors, the greatest drawback with tipranavir is its safety profile. The product has not been studied for an extended period of time. The clinical assessment was based on 24-week data from two pivotal studies.

Tipranavir is principally metabolized by the liver (CYP3A). Therefore, caution should be exercised when administering tipranavir to patients with hepatic impairment as tipranavir concentrations may be increased. Tipranavir is contraindicated in patients with moderate to severe (Child-Pugh class B and Child-Pugh class C) hepatic insufficiency.

Tipranavir contains a sulphonamide moiety; therefore, tipranavir should be used with caution in patients with a known sulphonamide allergy.

The most frequent adverse events in the clinical trials were diarrhea, nausea, fatigue, headache and vomiting. Diarrhea and nausea occurred in more than 10% of patients, and hypertriglyceridaemia, hyperlipidemia, anorexia, headache, vomiting, flatulence, abdominal distension, abdominal pain, loose stools, dyspepsia, rash, pruritus, and fatigue all occurred with an incidence between 1 and 10%.

Tipranavir has been associated with reports of clinical hepatitis and hepatic decompensation, including some fatalities. A causal relationship to tipranavir could not be established, however, all patients should be followed closely with clinical and laboratory monitoring, especially those who are co-infected with hepatitis B and/or C, as these patients have an increased risk of hepatotoxicity. Liver function tests should be performed prior to initiating therapy with tipranavir, and at regular frequent intervals throughout the duration of the treatment. Additionally, physicians and patients should be vigilant for the appearance of signs or symptoms of hepatitis, such as fatigue, malaise, anorexia, nausea, jaundice, bilirubinuria, acholic stools, liver tenderness or hepatomegaly. Patients with signs or symptoms of clinical hepatitis should discontinue tipranavir treatment immediately and seek medical attention.

Despite the safety issues identified, particularly for hepatically impaired patients, the efficacy associated with tipranavir for use as a salvage therapy makes it more than suitable. Aptivus has demonstrated a significant increase in efficacy such that the overall benefit/risk profile is improved for antiretroviral-experienced patients.

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 Aptivus, coadministered with low dose ritonavir, is favourable for combination antiretroviral treatment of HIV-1 infected adult patients with evidence of viral replication, who are treatment-experienced and have HIV-1 strains resistant to multiple protease inhibitors. 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	2005/04/08
Request for priority status	
Filed	2005/03/23
Approval issued by Director	2005/04/14
Submission filed	2005/05/09
Screening Acceptance Letter issued	2005/07/08
Review 1	
Quality Evaluation complete	2005/10/28
Clinical Evaluation complete	2005/11/08
Labelling Review complete	2005/11/08
NOC issued by Director General	2005/11/21