CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-307

PHARMACOLOGY REVIEW

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	22-307
SERIAL NUMBER:	000
DATE RECEIVED BY CENTER:	12/26/2007
PRODUCT:	Prasugrel HCl (Effient®) tablets, antiplatelet agent
INTENDED CLINICAL POPULATION:	Antithrombotic therapy in subjects with acute coronary syndrome
SPONSOR:	Eli Lilly & Co., Indianapolis, IN
DOCUMENTS REVIEWED:	Electronic submission, 12/26/2007
REVIEW DIVISION:	Cardiovascular and Renal Products, (HFD-110)
PHARM/TOX REVIEWER:	Belay Tesfamariam, PhD
CONCURRING REVIEWER:	Albert DeFelice, PhD
DIVISION DIRECTOR:	Norman Stockbridge, MD, PhD
PROJECT MANAGER:	Meg Pease-Fye
REVIEW PRIORITY:	Priority
DATE OF REVIEW SUBMISSION:	4/26/2008

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability:

The extent and scope of the pharmacological and toxicological documentation provided are appropriate to support the clinical use of prasugrel at daily oral dose of 10 mg.

B. Recommendation for nonclinical studies:

Adequate exposure was obtained in the toxicology studies, and all circulating metabolites in humans occurred in the circulation of species used in the nonclinical toxicity studies. The nonclinical studies adequately address the safety of prasugrel.

C. Recommendations on labeling:

The proposed prescribing information includes an appropriate description of the genotoxicity, animal carcinogenicity studies, developmental and reproductive studies, and appropriate advice on breast feeding.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings:

- Oral administration of prasugrel resulted in time- and dose-dependent inhibition of *ex vivo* platelet aggregation, *in vivo* thrombus formation and prolonged bleeding times.
- Following oral administration, prasugrel was rapidly absorbed and efficiently hydrolysed by esterases, and then metabolized by cytochrome P450 enzymes to form the active metabolite.
- Prasugrel metabolites identified in human plasma, urine, and feces were also identified in mice, rats and dogs. The metabolic pathway was similar in mice, rats, dogs and humans.
- Protein binding of prasugrel metabolites was similarly high (>80%) in the rat, dog, and human. Binding of the active metabolite, R-138727, was estimated to be 98% in human serum albumin solution.
- In the rat and dog, biliary excretion was the major route for elimination of prasugrel and its metabolites, and in mice elimination was mostly in the urine.
- At clinical doses, prasugrel is not expected to produce secondary pharmacodynamics related to central nervous system, cardiovascular (including *h*ERG assay), respiratory, renal, or gastrointestinal function.
- Toxicology studies identified the liver as a target organ as shown by increase in liver weight, hepatocellular hypertrophy, elevations of alkaline phosphatase activity and proliferation of smooth endoplasmic reticulum, which are consistent with the possibility of induction of hepatic drug metabolizing enzymes.

• Prasugrel caused induction of cytochrome P450 of phase I drug-metabolizing enzymes (primarily Cyp2B, Cyp3A2), and phase II drug-metabolizing enzymes. These observations are consistent with the decreases in exposure to prasugrel metabolites with multiple dosing and the morphologic hepatic changes suggest induction of drug metabolizing enzymes.

• No genetic toxicity was observed for prasugrel in standard tests that included an *in vitro* bacterial mutation test, Chinese hamster lung chromosomal aberration assay and *in vivo* mouse micronucleus test.

• In a 2-year rat carcinogenicity study, there was no evidence of excess treatment-related tumors with prasugrel exposures ranging to about 50 times the therapeutic exposures in humans. There was an increased incidence of hepatocellular adenomas in mice exposed for 2 years to high doses of about 190 times human exposure levels.

• In the rat and mouse, a non-neoplastic finding of a tendency for an increase in the incidence of eosinophilic altered cell foci was observed in the high dose groups. Thus, in the liver lesions, the tendency for an increase in the incidence of eosinophilic altered cell foci may be consequences of hepatic drug-metabolizing enzyme induction. It is considered that altered cell foci are progenitor lesions from which hepatocellular neoplasia might arise and some of the benign hepatocellular neoplasia may progress to malignant hepatocellular neoplasia. However, there was no evidence of malignant tumors in the 2-year rat and mouse studies of prasugrel.

• In the rat and mouse, there were high incidence of spontaneous carcinomas (liver, lung, thyroid, adrenal,) but these were not enhanced by treatment with prasugrel, which rules out possibility of tumor promoter effects.

• FDA computational quantitative structure activity relations by MC4PC or MDL-QSAR showed that prasugrel is not predicted to be carcinogenic, which is consistent with the negative carcinogenicity data of the *in vivo* rodent studies.

• Another member of the thienopyridine class, clopidogrel (plavix®), administered to rats for 104 weeks and mice for 78 weeks at plasma exposures >25 times than that in humans showed no evidence of tumorigenicity.

• Prasugrel did not cause any significant effects on fertility, early embryonic development, embryo-fetal development, or pre-/postnatal development in the rat or rabbit (approximately 30 times human exposure). At high doses causing effects on maternal body weight and/or food consumption, there was a slight decrease in offspring body weight relative to controls. Placental transfer of prasugrel metabolites to the fetus of pregnant rats was low. ^{14}C-prasugrel was excreted in the milk of lactating rats.

• Adequate margins of safety were established based on exposure to the active metabolite (R-138727), and to the primary human metabolite (inactive, R-106583) in the toxicology studies.

B. Pharmacologic activity:

• Prasugrel is a prodrug whose active metabolite specifically and irreversibly inhibit the $P2Y_{12}$ purinergic receptor, and consequently inhibits ADP-mediated platelet aggregation.

• Oral administration of prasugrel resulted in inhibition of *ex vivo* platelet aggregation, *in vivo* thrombus formation and prolonged bleeding times.

• Additive or synergistic platelet inhibitory effects that result from co-administration of prasugrel and aspirin were demonstrated in several studies of platelet aggregation (*ex vivo*), thrombus formation (*in vivo*) and bleeding times.

• Prasugrel is approximately 10- and 100-fold more potent than clopidogrel and ticlopidine, respectively, in inhibiting platelet aggregation, thrombus formation and prolonging bleeding times.

• The antiplatelet effects of the active metabolites of prasugrel and clopidogrel are approximately equipotent *in vitro*. Accordingly, the difference for the *in vivo* potency of the parent molecules appears to be related to increased efficiency in the formation of the active metabolite of prasugrel, and the consequent higher exposure to the active metabolite. Thus, the greater pharmacodynamic response for prasugrel was a result of more extensive formation of its active metabolite compared to clopidogrel.

• The plasma exposure levels of metabolites after oral administration of prasugrel HCl salt was slightly higher (about 20-30%) compared with the prasugrel free base formulation.

• Plasma concentrations of prasugrel metabolites from both formulations of the free base and HCl salt of prasugrel were reduced treatment with the proton pump inhibitor, lansoprazole, indicating that increasing the gastric pH reduced the rate of generation of prasugrel's active metabolite. This suggests that dose adjustment of prasugrel may be warranted during treatment with proton pump inhibitors.

• Plasma concentrations of prasugrel metabolites from orally administered free base and HCl salt forms were reduced (by 65% and 30%, respectively) by treatment with the histamine H_2 receptor blocker, ranitidine, suggesting that increasing stomach pH could decrease the absorption of prasugrel. Because the pH effects were less for HCl salt form, it was selected for further development.

C. Nonclinical safety issues relevant to clinical use:

• The most prominent toxicology findings are hepatocellular hypertrophy, increase liver weight, elevation of ALP activity and proliferation of smooth endoplasmic reticulum consistent with hepatic metabolizing enzyme induction.

• Prasugrel causes induction of cytochrome P450 of phase I and phase II drug-metabolizing enzymes, which is consistent with the decreases in exposure to prasugrel metabolites after multiple dosing. No specific animal studies have been conducted on the effects of induction of drug metabolizing enzymes and interaction with other drugs metabolized via Cyp2B and cyp3A.

• Comparative 1-month toxicity studies in the rat with prasugrel and clopidogrel demonstrated similar toxicity profiles including increase in liver weight, ALP and Cyt P_{450}, proliferation of liver SER and hypertrophy of follicular epithelium in thyroid.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 22-307

Sequence number/date: 000 / 12/26/2007
Information to sponsor: Yes ( ) No (√)
Sponsor: Eli Lilly & Co., Indianapolis, IN
Manufacturer for drug substance: Eli Lilly & Co., and Daiichi Sankyo Co., Ltd.

Reviewer name: Belay Tesfamariam, Ph.D.
Division name: Cardiovascular and Renal Products, HFD #: 110
Review completion date: 4/26/2008

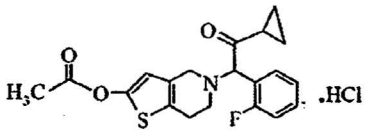
Drug:

Trade name: Effient®
Generic name: Prasugrel HCl
Code name: CS-747 (R-91220)
Chemical name: 2-Acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride

CAS registry number: 389574-19-0

Molecular formula: $C_{20}H_{20}FNO_3S.HCl$; Molecular weight: 409.9

Structure:



Relevant NDA: # 020839, Clopidogrel (Plavix®)

Drug class: ADP receptor antagonist ($P2Y_{12}$ purinergic receptor).

Intended clinical population: Antithrombotic agent in subjects with acute coronary syndrome (percutaneous coronary intervention, coronary angioplasty, Coronary artery bypass).

Clinical formulation: Tablets (10 mg).

Route of administration: Oral

Disclaimer: Tabular and graphical information are constructed by the sponsor unless cited otherwise.

Studies reviewed within this submission: Pharmacology, pharmacokinetics, toxicology, genotoxicity, carcinogenicity, reproductive toxicity.

Studies not reviewed within this submission: None

2.6.2 PHARMACOLOGY

Prasugrel is a prodrug that is de-esterified to form an active metabolite which irreversibly inhibits platelet $P2Y_{12}$ purinergic receptor. Prasugrel is an inhibitor of adenosine 5'-diphosphate (ADP)-induced platelet aggregation by the inhibition of ADP binding to its receptor, and the subsequent activation of the glycoprotein GPIIb/IIIa complex, and prolongs bleeding times. Prasugrel has been shown to be efficacious as an antithrombotic agent in an electrically-induced thrombosis animal model, and is at least 10-times more potent than clopidogrel. Superior levels of platelet inhibition may translate into greater antithrombotic efficacy in the clinic.

2.6.2.1 Brief summary

ADP plays a key role in initiating platelet aggregation in both normal hemostasis and pathologic thrombotic disorders. Aggregated platelets may lead to platelet-rich thrombi, vascular occlusion, tissue ischemia, and myocardial necrosis in what is collectively known as acute coronary syndromes. The importance of ADP in the pathogenesis of arterial thrombosis is supported by the demonstration that ADP receptor antagonists, such as clopidogrel and ticlopidine, are effective in reducing thromboembolic events, and the reduction of stent thrombosis in acute coronary syndromes. These drugs have limitations in terms of their adverse effects including neutropenia and thrombocytopenic purpura. The goal is to develop a potent antiplatelet drug that is selective against the $P2Y_{12}$ purinergic receptor, with a relatively rapid onset of action, and exhibit fewer side effects compared with clopidogrel.

2.6.2.2 Primary pharmacodynamics

Prasugrel, a member of thienopyridine class of antiplatelet agents, is an inhibitor of platelet aggregation by direct antagonism of ADP binding to $P2Y_{12}$ receptors.

Mechanism of action: Prasugrel is a prodrug that is de-esterified to form an active metabolite R-138727, which irreversibly inhibit platelet $P2Y_{12}$ purinergic receptor, and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex.

Drug activity related to proposed indication

Prasugrel on bleeding time in rat model:

Single or repeated 3-day oral administrations of prasugrel (CS-747), clopidogrel and ticlopidine prolonged the bleeding time in a dose-dependent manner in the rat tail transaction model (Figure 1). The dose that doubles the bleeding time values of prasugrel, clopidogrel and ticlopidine were 0.14, 1.8, and 75 mg/kg, respectively. The ED_{50} values following 3-day oral administration of prasugrel, clopidogrel and ticlopidine for ADP (3 μM)-induced *ex vivo* rat platelet aggregation were 0.54, 6.2 and 300 mg/kg/day, respectively. Prasugrel was 12 times more potent than clopidogrel, and > 100 times more potent than ticlopidine in prolonging the bleeding time.

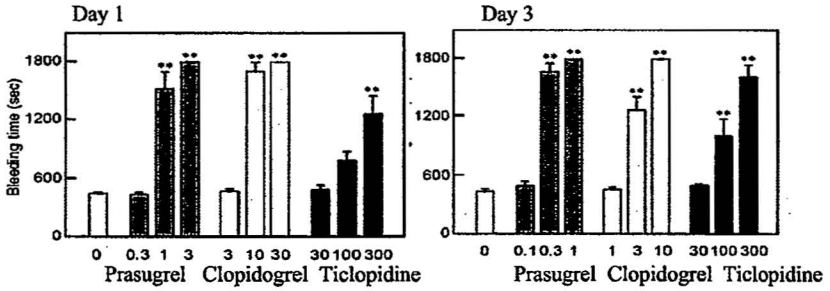


Figure 1. Bleeding time effects of single (left panel) and 3-day (right panel) repeated administration of prasugrel, clopidogrel and ticlopidine (mg/kg, *p.o.*) in rat tail transection model (n=7).

Prasugrel on thrombus formation in rat arterio-venous shunt model:

Single oral dose of prasugrel (0.1 - 3 mg/kg) prevented thrombus formation in a dose-dependent manner with an ED_{50} value of 0.68 mg/kg in the rat arterio-venous shunt thrombosis model (Figure 2, left panel). Clopidogrel (1 - 30 mg/kg, *p.o.*) also showed antithrombotic effects, but its efficacy was less potent compared to prasugrel; the ED_{50} for clopidogrel was 6.3 mg/kg (*p.o.*) (Figure 2, right panel), indicating that prasugrel has a potent antithrombotic activity.

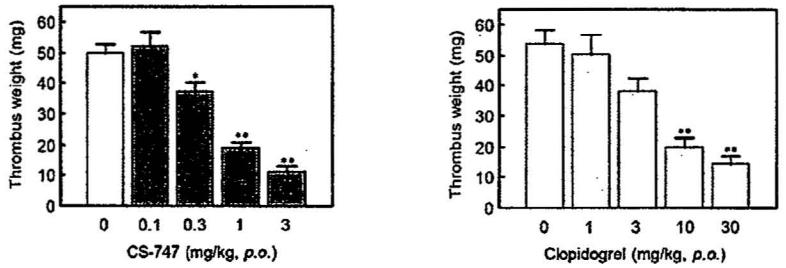


Figure 2. Antithrombotic effects of CS-747 (prasugrel, left panel) and clopidogrel (right panel) in arterio-venous shunt thrombosis model in rat (n=6).

Prasugrel on time to occlusion in rat carotid artery electrical injury model:

In the rat carotid artery electrical stimulation-induced thrombosis model, the time to occlusion and duration of patency were prolonged by prasugrel, clopidogrel and ticlopidine in dose-dependent manner (Figure 3). The antithrombotic activity of prasugrel was at least 10-times more potent than clopidogrel, and 100-times more potent than ticlopidine.

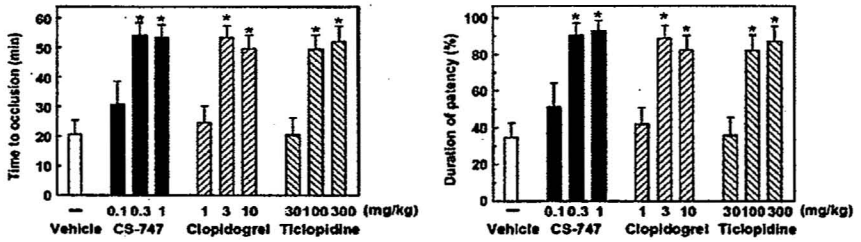


Figure 3. Antithrombotic effects of CS-747 (prasugrel), clopidogrel and ticlopidine administered orally for 3 days in an electrically-induced thrombosis rat carotid artery model. Each column shows time to occlusion (left panel) and the duration of patency (right panel) (n=8).

Inhibitory effects of prasugrel on platelet aggregation in cynomolgus monkeys:

Repeated oral administration of prasugrel to the cynomolgus monkey showed potent and long-lasting antiplatelet effect, demonstrating its antithrombotic activity (Figure 4). The inhibitory effects of prasugrel reached a steady state on Day 3 to 5, indicating its cumulative effects.

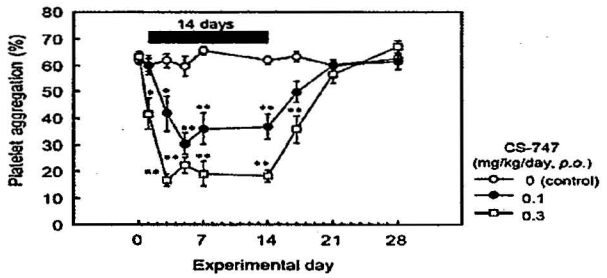


Figure 4. Inhibition of ADP (10 μM)-induced *ex vivo* platelet aggregation in 14-day repeated oral administration of CS-747 (prasugrel) in cynomolgus monkey (n=5).

Intravenous *vs.* oral administration of prasugrel on platelet aggregation in rats:

Intravenous injection of prasugrel free base (0.3 - 3 mg/kg) resulted in inhibition of ADP-induced platelet aggregation in a dose- and time-related manner (Figure 5, left panel). Oral administration of prasugrel HCl salt (1 - 10 mg/kg) inhibited ADP-induced platelet aggregation in a dose- and time-dependent manner, but the potency was less than that of an intravenous injection of prasugrel (Figure 5, right panel). At the same dosage of prasugrel (*i.v.*) and prasugrel HCl (*p.o.*), the time required to achieve 50% inhibition (ED_{50}) of platelet aggregation for intravenous injection of prasugrel was less than that for oral administration of prasugrel HCl (Figures 5). These results suggest that intravenous injection of prasugrel free base shows more a potent and faster onset of antiplatelet activity than oral administration of prasugrel HCl.

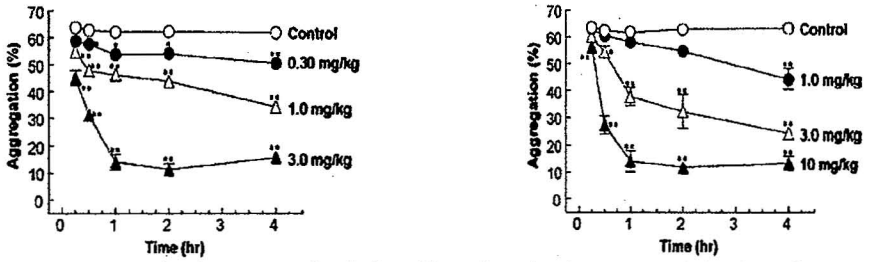


Figure 5. *Ex vivo* platelet aggregation induced by ADP after intravenous injection of prasugrel free base (left panel), and oral administration of prasugrel HCl salt (right panel) to rats (n=6).

Comparison of prasugrel and clopidogrel in inhibition of platelet aggregation in rats:

Orally administered prasugrel (0.3 - 3 mg/kg) and clopidogrel (3 - 30 mg/kg) inhibited ADP-induced platelet aggregation in a dose-dependent manner, and prasugrel was 13 times more potent than clopidogrel (Figure 6). The maximum inhibition of platelet aggregation for prasugrel was observed at 4 hr after dosing with an ED_{50} of 1.2 mg/kg, Clopidogrel had a slightly slower onset of action. The plasma concentrations of R-138727 (primary prasugrel active metabolite) was higher than R-130964 (primary clopidogrel active metabolite) even though 10-times higher doses of clopidogrel were used suggesting that R-138727 was generated more efficiently compared to R-130964. The antiplatelet effects of prasugrel and clopidogrel are dependent on the amount of active metabolites generated, and that the more efficient *in vivo* production of the prasugrel active metabolite may account for its potent antiplatelet activity.

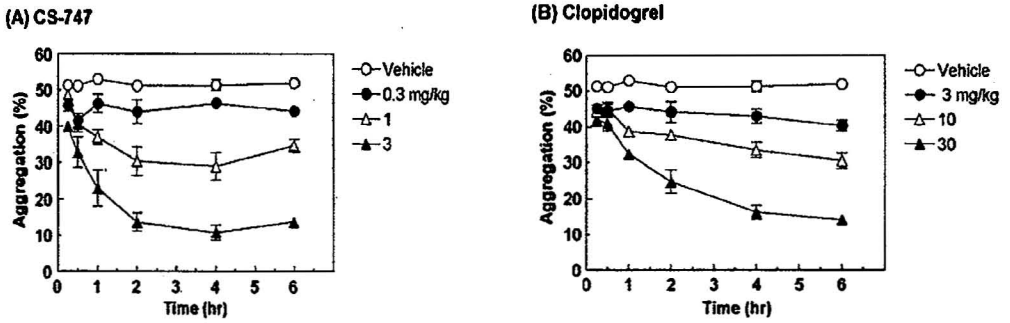


Figure 6. *Ex vivo* ADP-induced platelet aggregation in rats treated with CS-747 (prasugrel, panel A) and clopidogrel (panel B) (n=5).

Comparison of active metabolites of prasugrel and clopidogrel:

The two active metabolites of prasugrel (R-99224) and clopidogrel (R-130964) have similar concentration-dependent potency against ADP- or the stable ADP analogue 2Me-S-ADP-induced human platelet aggregation (Figure 10). These data suggest that the *in vivo* and *ex vivo* differences in potency of prasugrel and clopidogrel do not reflect differential activity of their active metabolites, rather greater exposure to prasugrel as active metabolite underlies its greater *in vivo* potency.

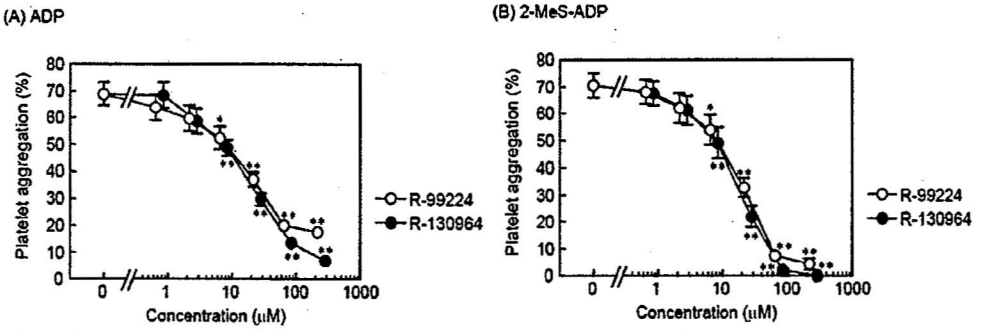


Figure 7. Inhibition of platelet aggregation by active metabolites R-99224 (prasugrel) and R-130964 (clopidogrel) in ADP (panel A) and 2Me-S-ADP–induced (panel B) human platelets.

In vitro effects of prasugrel active metabolites on platelet aggregation:

Like clopidogrel, prasugrel is inactive *in vitro*. The pharmacological action of prasugrel after its administration is due to the formation of an active metabolite, collectively referred to as R-138727. Among the hepatic metabolites, R-99224 is a mixture of two of the possible four steoisomers of R-138727 and has an *in vitro* activity similar to the *ex vivo* activity of prasugrel. R-99224 inhibited platelet aggregation in a concentration-dependent manner *in vitro* platelet-rich plasma from humans, monkeys, dogs, rabbits, and rats at IC_{50} values of 15, 32, 7.3, 22 and 45 pM, respectively (Figure 7). In contrast, prasugrel, even at the highest concentration (300 pM), showed minimal effects in rat and human platelet aggregation *in vitro* (Figure 7).

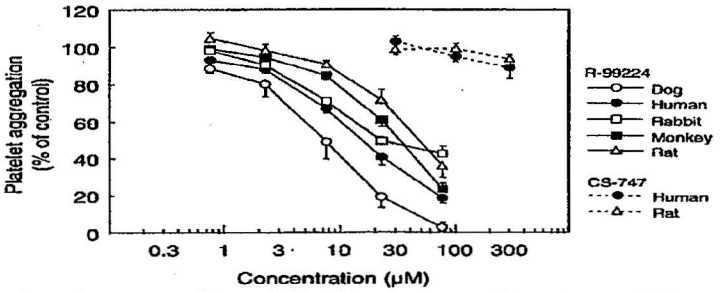


Figure 8. *In vitro* effects of CS-747 (prasugrel) and its active metabolite mixture, R-99224, on ADP-induced platelet aggregation in platelets from humans, dogs, rabbits and rats.

Potency comparison of the four stereoisomers comprising R-138727:

R-9224 is a mixture of two enantiomers R-125688 and R-125690. R-100364, the diastereomer of R-99224, is a mixture of the two enantiomers R-125687 and R-125689. Collectively these four sterioisomers that comprise the active metabolite are known as R-138727. *In vitro* assay of the four stereoisomers caused inhibition of ADP-induced human platelet aggregation in a concentration-dependent manner, with the following rank order of potency: R-125690 > R-125689 > R-125687 = R-125688 with an IC_{50} values of 0.19, 3.1, 28 and 36 μM, respectively (Figure 9). These results show that R-125690 has the most potent antiplatelet activity among these four stereoisomers.

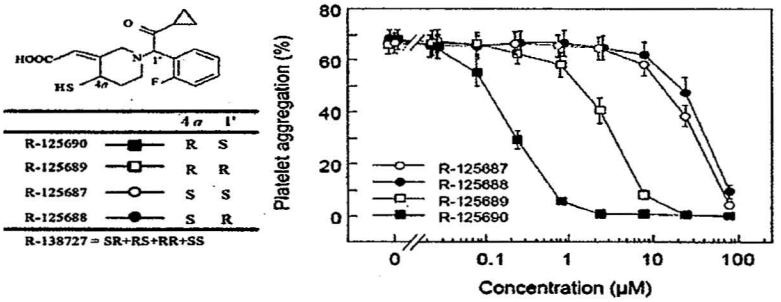


Figure 9. *In vitro* effects of 4 sterioisomers of the active metabolite R-138727 on ADP (10 μM) induced human platelet aggregation