ABSTRACT:

Clopidogrel hydrogen sulfate, a thienopyridine derivative, is an ADP receptor antagonist that inhibits platelet aggregation. Clopidogrel is an enantiopure carboxylic ester of \( \text{S} \)-configuration. The \( \text{R} \)-enantiomer is devoid of antithrombotic activity and can provoke convulsions at high doses in animals. During preclinical safety evaluation, the possible chiral inversion of clopidogrel has, therefore, been investigated in vivo after repeated oral administration of different dose levels of clopidogrel to male and female rats. Due to rapid metabolism in the liver and low plasma levels of unchanged drug, possible chiral inversion was assessed by monitoring the plasma concentrations of the carboxylic acid metabolites, i.e., the \( \text{(S)} \)- and \( \text{(R)} \)-acid, by means of a stereoselective assay. The production of 4 to 8% of \( \text{(R)} \)-acid was observed. This could be the result of chiral inversion of either clopidogrel or its main metabolite, the \( \text{(S)} \)-acid. Thus, the possibility of nonenzymatic and enzymatic inversion of clopidogrel and its carboxylic acid metabolite was studied in vitro by chiral HPLC and \(^{1}H \) NMR. Nonenzymatic chiral inversion of clopidogrel at \( 37^\circ \text{C} \) in \( 0.1 \) M phosphate buffers could be observed but was found to be slow, with estimated half-lives of 7 to 12 days, depending on the pH. The \( \text{(S)} \)-acid was configurationally fully stable up to 45 days in phosphate buffers. Neither clopidogrel nor its carboxylic acid metabolites were subject to enzymatic chiral inversion in isolated rat hepatocyte suspensions. We conclude that the nonenzymatic inversion of clopidogrel accounts for the 4 to 8% of chiral inversion seen in vivo in the rat.
in vivo after repeated oral administration of different dose levels of clopidogrel hydrogen sulfate to male and female rats. Because of the low plasma levels of unchanged drug (Herbert et al., 1993), a possible chiral inversion of clopidogrel was assessed by monitoring the plasma concentrations of its carboxylic acid derivatives with S- and R-configuration, using a stereoselective assay. To get further insights, the nonenzymatic (i.e., chemical) inversion of clopidogrel was studied by chiral HPLC and by $^1$H NMR [$^1$H/H substitution according to Kawaszoe and Ohnishi (1964), Testa (1973), Reist et al. (1995, 1996)], and the effects of pH, buffer concentration,ionic strength, and polarity of the solvent were examined. The configurational stability of the (S)-acid was verified by $^1$H NMR, although its nonenzymatic inversion is highly improbable, because a free carboxy group is known to strongly increase the configurational stability of chiral carbon atoms of the type R$^R$RC-H (Testa et al., 1993; Reist et al., 1997). The enzymatic inversion of clopidogrel and its carboxylic acid derivatives was investigated in isolated rat hepatocyte suspensions. A number of anti-inflammatory 2-arylpropionic acids are well known to invert configuration via their CoA\textsuperscript{1} thioester conjugate (Knihiinni et al., 1989; Mayer, 1990). Thus, the possibility that the (S)- and/or (R)-acid metabolites of clopidogrel invert via a similar mechanism was investigated.

### Materials and Methods

**Chemicals.** Clopidogrel hydrogen sulfate, the hydrogen sulfate of its R-enantiomer, and the hydrochlorides of their carboxylic acid derivatives [(S)- and (R)-acid] were supplied by Sanofi Recherche (Montpellier, France). Their optical purities were 98.9, 98.2, 94.3, and 95.2%, respectively, α-(2-Methylphenyl)-6,7-dihydroxy-3,4,2-c-pyridin-5(4H)-acetic acid was also supplied by Sanofi Recherche. (S)-(−)-Ibuprofen was generously donated by the Boots Co. Ltd. (Nottingham, England). BSA (fraction V) was purchased from Fluka Chemie AG (Buchs, Switzerland). Collagenase (Clostridium histolyticum type IV), EGTA, (S)−−−− α-(1-naphthyl)ethylamine (enantioselective excess >98%), 1-hydroxybenzotriazole (HOBT), and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDAC) were obtained from Sigma Chemical Co. (St. Louis, MO). The deuterated solvents were purchased from Armar (Döttingen, Switzerland), and their isotopic purities were: D$_2$O 99.8 atom%D, DMSO-$_d_6$ 99.8 atom%D, and CD$_3$CN 99.8 atom%D. All other chemicals were of analytical grade and used without further purification.

**In Vivo Chiral Inversion in Rats.** Animals. This study was conducted with the principles of Good Laboratory Practice. At the beginning of the treatment period, Crl CD (SD) BR rats (Charles River, Saint-Aubin-les-Elbeuf, France) were approximately 6 weeks old and had mean body weights of 192 g and 159 g for males and females, respectively. During the study, the animals were housed in suspended wire-mesh cages (43.0 × 21.5 × 18.0 cm), and each cage contained two rats of the same sex and group. The animal rooms had a temperature range of 19–23°C, a relative humidity range of 30 to 70%, and a light/dark cycle of 12 h. Animals had free access to diet (A04 C diet, U.A.R., Villemoisson-sur-Orge, France) and to tap water filtered with a 0.22-μm filter (Millipore S.A., Vélizy, France).

Study design. After clinical examination to ensure animals were in good health, 96 male and 96 female rats were assigned to four experimental groups receiving different levels of clopidogrel hydrogen sulfate (10, 35, 100, and 160 mg/kg/day). The drug was administered in the diet during 4 weeks. The concentration of clopidogrel hydrogen sulfate in the diet was modified every week according to body weight and food consumption data, to maintain the adequate dose levels for each group. To determine the exposure at steady-state after 4 weeks, blood samples were collected every 3 h from day 27 at 7:00 PM to day 28 at 7:00 PM, i.e., on day 27 at 7:00 and 10:00 PM, and on day 28 at 1:00, 4:00, 7:00, and 10:00 AM and at 1:00, 4:00, and 7:00 PM. AUC$_{0-24h}$ values were calculated from 7:00 PM on day 27 to 7:00 PM on day 28. This 24-h period corresponded to a light/dark cycle (12 h/12 h) in animal rooms. At each sampling time, blood samples were collected from four individual males and four individual females per experimental group. To reduce the total number of animals, for half of the rats per group, two blood samples were withdrawn from the same animal with an interval period of 12 h. Blood was collected in tubes containing lithium heparin as an anticoagulant, from the orbital sinus of the animals under slight ether anesthesia. After centrifugation, plasma samples were stored at −20°C until assayed for (S)-acid and (R)-acid.

**Analytical method.** After addition of α-(2-methylphenyl)-6,7-dihydroxy-3,4,2-c-pyridin-5(4H)-acetic acid as internal standard (5 μg), the stereoselective analysis of the (S)-acid and (R)-acid was carried out as follows. The extraction and derivatization procedures were modifications of the method of Hutt et al. (1986). Briefly, to an aliquot of plasma (0.25 ml) acetate buffer, pH 5 (0.75 ml), and acetonitrile (0.25 ml) were added. This solution was placed on the top of an Extrelut-1 column (Merck, Darmstadt, Germany). A first elution with hexane (5 ml) was discarded, and analytes were eluted with CH$_2$Cl$_2$ (5 ml). After evaporation of the solvent, the dry residue was reconstituted in CH$_2$Cl$_2$ (1 ml) and derivatized with (S)-α-(1-naphthyl)ethylamine (0.1 ml of a 0.1 mg/ml solution in CH$_2$Cl$_2$) in the presence of HOBT (0.1 ml of a 1.5 mg/ml solution in CH$_2$Cl$_2$) and EDAC (0.1 ml of a 1.5 mg/ml solution in CH$_2$Cl$_2$). After a 16-h incubation at room temperature, water (4 ml) and hexane (3 ml) were added. The two phases were separated, and the organic phase reduced to dryness at room temperature under a stream of nitrogen. The dry residue was dissolved in the HPLC mobile phase (20 μl).

The 1-naphthylethylamide derivatives of (S)- and (R)-acid were separated on a Hypersil ODS 5 μm stationary phase (250 mm × 4 mm; Lichrocart, Merck, Darmstadt, Germany). The mobile phase consisted of acetonitrile/ triethylammonium acetate buffer, pH 3.3, 0.01 M (55:45, v/v) delivered at a flow rate of 1.25 ml/min. Spectrofluorimetric detection was performed at excitation and emission wavelengths of 280 and 330 nm, respectively. Linearity over the standard range [0.60–40 mg/l for (S)-acid and 0.06–4 mg/l for (R)-acid] was shown. The interday coefficients of variation for (S)-acid at concentrations of 0.60, 6.0, and 40 mg/l were 4.3, 6.0 and 4.6%, and those for (R)-acid at concentrations of 0.06, 0.60 and 4.0 mg/l were 8.0, 8.4, and 4.3%. The retention times of the amides of the (S)- and (R)-acid were about 26 and 32 min, respectively.

**Data analysis.** Concentrations of (S)- and (R)-acid were expressed as unsalified compounds. On days 27 and 28, population estimates of AUC$_{0-24h}$ and their standard errors were calculated for each dose level by sex combination using the linear trapezoidal rule on average concentration at each sampling time (Yeh, 1990). Considering the composite design adopted for blood sampling, the terminology “population estimates” has been used. For all estimates, 95% confidence intervals were calculated from the standard error of the estimate, and degrees of freedom were determined using the Satterthwaite procedure.

Analyses were performed using the GLM and IML procedures in the SAS statistical software package (version 6.09) (SAS Institute Inc., Cary, NC) and macro DISTRICT3 of the biosistatistics program.

**Nonenzymatic Chiral Inversion and Hydrolysis Monitored by HPLC.** In aqueous solutions at physiological pH, clopidogrel hydrogen sulfite is very slightly soluble (<0.001 mg/ml), and a co solvent (methanol) had to be used to investigate its nonenzymatic chiral inversion and hydrolysis by HPLC.

Three mixtures of methanol with phosphate buffer pH 7.4 (0.2 M, ionic strength 0.52), in the proportions 1:1, 2:3, and 1:2 (v/v) were prepared to assess the influence of methanol concentration. The influence of pH was investigated by measuring reaction rates in 1:1 (v/v) mixtures of methanol and phosphate buffers (0.1 M, ionic strength 0.3) of four different pH values, pH 3.0, 5.6, 7.4, and 9.0. To study the influence of buffer concentration, 1:1 (v/v) mixtures of methanol and phosphate buffers (pH constant at 7.4, ionic strength 0.78) of three different concentrations (0.1, 0.2, and 0.3 M) were prepared. Mixtures of two (1:1, v/v) of methanol and phosphate buffers (pH 7.4, 0.2 M) of three different ionic strengths (0.52, 0.6, 0.78) were prepared to investigate the influence of ionic strength.

Clopidogrel hydrogen sulfite (30 mg, 7.738 × 10$^{-3}$ M) was dissolved in 100 ml of the solvent mixtures described above. Each solution was placed in a 100-ml bottle with a crown cap and kept in a rotating water bath at 37±...
0.2°C. Kinetic studies were performed by repeated sampling of 0.2-ml reaction mixture followed by HPLC analysis over a time interval of 78 days.

To observe a possible esterification of the (S)-acid, 1:1 (v/v) mixtures of methanol and phosphate buffers (0.1 M, ionic strength 0.3) of pH 7.4 and pH 9.0 were prepared. The (S)-acid hydrochloride (30 mg, 8.309 × 10⁻³ M) was dissolved in 100 ml of solvent mixture, and the solutions were handled like the clopidogrel solutions. Analyses were performed over a time interval of 42 days.

**Analytical methods.** To monitor chiral inversion, clopidogrel and its enantiomer were separated on a Nucleodex t 4.6 mm (Macherey-Nagel, Düren, Germany), using the mobile phase methanol/triethylammonium acetate buffer, pH 7.5, 0.01 M (70:30, v/v) plus decylamine 0.01 M, a flow rate of 0.7 ml/min, and UV detection at 230 nm. The retention times of clopidogrel and its enantiomer were 19.1 and 22.1 min, and the detection limits were 2 and 2.5 mg/l, respectively.

To monitor either the hydrolysis of clopidogrel or the esterification of the (S)-acid, a nonstereospecific assay method was used. Clopidogrel plus its enantiomer and the two carboxylic acid derivatives [(S)-acid plus (R)-acid] were separated on a Supelcosil LC-ABZ column 150 × 4.6 mm (Supelco, Gland, Switzerland) using the mobile phase methanol/phosphate buffer, pH 7.5, 0.01 M (70:30, v/v) plus decylamine 0.01 M, a flow rate of 0.8 ml/min, and UV detection at 230 nm. The retention times of the acids and esters were 4.5 and 9.2 min, and the detection limits were approximately 1 and 2.5 mg/l, respectively.

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Systemic pharmacokinetics of the (S)-acid and (R)-acid determined from day 27 7:00 PM to day 28 7:00 PM after repeated oral (admixture with diet) administration of clopidogrel hydrogen sulfate to rats

Results

In Vivo Chiral Inversion in Rats. Clopidogrel hydrogen sulfate administered orally (in the diet) to rats at dose levels of 10, 35, 100, and 160 mg/kg/day over a 4-week period was well tolerated by all animals, and no clinical signs of adverse reaction to the treatment were observed. From food consumption, the achieved dosages were in good agreement with the nominal dosage for each sex and at all dose levels, throughout the study. Overall mean values were 10.2, 35.2, 100.4, and 160.7 mg/kg/day in males, and 9.8, 33.6, 96.7, and 154.5 mg/kg/day in females.

Due to low plasma levels of unchanged drug (Savi et al., 1992, 1994), its carboxylic acid derivatives have been used as surrogate marker for the possible chiral inversion of clopidogrel. Values for $C_{\text{max}}$ (maximal plasma concentration) and AUC$_{0-24\ h}$ (area under the plasma drug concentration-time curve for 24 h) of both acid enantiomers determined after 4 weeks are given in Table 1. From mean AUC values, the contribution of the (R)-acid to the total acid exposure was 6.4, 5.8, and 4.9% in male rats at 35, 100, and 160 mg/kg dose levels, respectively, and 7.6, 4.7, and 3.7% in female rats at 35, 100, and 160 mg/kg dose levels, respectively. (R)-Acid contribution was constant over the dosing interval. Thus, 4 to 8% of (R)-acid could be detected in the plasma of all animals, independent of sex.

Nonenzymatic Chiral Inversion and Hydrolysis Monitored by HPLC. Estimated half-lives of nonenzymatic chiral inversion and hydrolysis of clopidogrel in the investigated media were between 3.5 and 8.5 weeks, and 3 and 36 months, respectively. The influences of methanol concentration, pH, phosphate concentration, and ionic strength on the rate constants of chiral inversion and hydrolysis are shown in Table 2. The rates of inversion and hydrolysis decreased with increasing methanol concentration and were pH-dependent. The chiral inversion was slower in acidic solutions than in neutral or basic media, and the hydrolysis showed a minimum at a pH around 5 and increased in acidic and in alkaline media. The rates of both reactions were proportional to the phosphate concentration.

By extrapolating the results obtained to 0% methanol concentration, rate constants of chiral inversion and hydrolysis of clopidogrel at 37°C in phosphate buffers of various pH values were estimated. The estimated rate constants and $t_{90}$ values, for 10% hydrolysis or chiral inversion, are summarized in Table 3.

No esterification of the (S)-acid in the investigated 1:1 (v/v) mixtures of methanol and phosphate buffers of pH 7.4 and 9.0 was observed up to 42 days.

Nonenzymatic Chiral Inversion Monitored by $^1$H NMR. $^1$H NMR has previously been shown to be a suitable tool to assay inversion of chiral centers of the type R$^R$/R$^R$/RC-H (Kawazoe and Ohnishi, 1964; Testa, 1973; Reist et al., 1995, 1996). The rates of deuteration of clopidogrel in different solvents at 37°C are shown in Table 4. Deuteration and, therefore, chiral inversion of clopidogrel in all solvents were found to be low. In fact, the estimated half-lives of deuteration were between 1 and 8 months.

\[
\begin{array}{cccc}
\text{Parameter} & \text{Dose Level} & (S)-Acid & (R)-Acid \\
& \text{mg/kg/day} & \text{Males} & \text{Females} & \text{Males} & \text{Females} \\
C_{\text{max}} (\text{mg/l}) & \text{10} & 2.3 \pm 1.0 & 0.97 \pm 0.01 & <0.060 & <0.060 \\
& 35 & 5.2 \pm 1.9 & 2.9 \pm 0.75 & 0.3 \pm 0.10 & 0.3 \pm 0.05 \\
& 100 & 23.6 \pm 5.8 & 14.3 \pm 1.9 & 1.1 \pm 0.20 & 0.8 \pm 0.39 \\
& 160 & 27.6 \pm 3.3 & 30.4 \pm 6.8 & 1.3 \pm 0.40 & 1.2 \pm 0.15 \\
& 35 & 77 \pm 14 & 55.6 \pm 5.8 & NA & NA \\
& 100 & 356 \pm 50 & 236 \pm 20 & 20.6 \pm 2.0 & 11.1 \pm 1.3 \\
& 160 & 498 \pm 59 & 513 \pm 46 & 24.5 \pm 2.2 & 19.0 \pm 0.6 \\
AUC$_{0-24\ h}$ (mg h/l) & \text{10} & 23.6 & 2.3 & 6.4 & 5.8 & 4.9 \\
& 35 & 356 & 14.3 & 10.2 & 35.2 & 100.4 & 160.7 \\
& 100 & 96.7 & 154.5 \\
& 160 & 59 & 513 & 46 & 22.2 & 19.0 \\
\end{array}
\]
The investigation of the deuteration (i.e., chiral inversion) of the (S)-acid of clopidogrel showed no disappearance of the signal of the proton coupled to its chiral center (singlet around 5.3 ppm). Because the detection limit of the method by \(^1\)H NMR used was 0.1 mg/ml, it can be deduced that in 45 days less than 0.5% inversion occurred. Hence, the configuration of the (S)-acid can be considered as stable up to 45 days in all media studied.

**Enzymatic Chiral Inversion and Hydrolysis in Rat Hepatocyte Suspensions.** Incubations of clopidogrel. Isolated rat hepatocytes were incubated with different concentrations of clopidogrel (25, 50, and 100 mg/l) and the formation of the (S)- and (R)-acid was monitored. Only the (S)-acid, the carboxylic acid derivative with the same configuration as clopidogrel, was detected at all concentrations investigated. The concentration of the (S)-acid increased with time and reached maximal levels of 7 to 15 mg/l, depending on the initial concentration of clopidogrel. Because the detection limit of each enantiomer in the incubation medium was 0.2 mg/l, it can be deduced that there was less than 1 to 2% of chiral inversion of clopidogrel occurring in rat hepatocyte suspensions.

The hydrolysis of clopidogrel in rat hepatocyte suspensions is illustrated in Fig. 2, showing the rapid decrease of clopidogrel (25 mg/l) with a simultaneous increase in concentration of the (S)-acid. The rate of hydrolysis of clopidogrel (\(k_{AB} = 0.52 \pm 0.028 \text{ h}^{-1}\)) is slower than its nonhydrolysis elimination (\(k_A = 0.82 \pm 0.049 \text{ h}^{-1}\)). In rat hepatocyte suspensions, approximately 39% of the initial concentration of clopidogrel was hydrolyzed to its carboxylic acid metabolite with S-configuration. It can further be noted that the time-concentration profile of (S)-acid after incubation of 25 mg/l of clopidogrel, determined with the nonstereoselective method, was identical to that obtained with the stereoselective method.

**Incubations of the (S)-acid and (R)-acid.** At incubations of either the (S)-acid or (R)-acid (10 mg/l) no formation of the antipodes could be detected during the 4 h of incubation, indicating a lack of enzymatic inversion of (S)-acid to (R)-acid or vice versa. The elimination of the acids was of first order, and no significant difference in the rates of elimination of the enantiomers was observed. Indeed, the elimination rate constants were 0.25 \(\pm\) 0.010 and 0.26 \(\pm\) 0.015 h\(^{-1}\) for the (S)- and (R)-acid, respectively.

**Discussion**

Daily oral administration of different dose levels of clopidogrel (10–160 mg/kg/day) over a 4-week period to male and female rats resulted in production of 4 to 8% of the (R)-acid, the carboxylic acid derivative with configuration opposite to that of clopidogrel. Indeed, plasma levels of the (S)-acid were 2- to 25-fold higher than those of (R)-acid. Despite the fact that, at the 100 mg/kg/day dose level, the (R)- and (S)-acid AUC values were significantly greater for males than for females, a finding that deserves confirmation, the contribution of (R)-acid was independent of sex and constant over the dosing interval. This observed appearance of a small percentage of (R)-acid in the plasma could be the result of nonenzymatic or enzymatic chiral inversion of either clopidogrel or its main metabolite, the (S)-acid. To address this question further, investigations in vitro on the mechanism of chiral inversion of clopidogrel and its carboxylic acid derivatives were performed.

The nonenzymatic chiral inversion and hydrolysis of clopidogrel in all investigated media were found to be slow. Both rates of reaction were pH-dependent and decreased with increasing methanol concentration. These findings are in good agreement with the fact that inversions of chiral centers of the type R’R’/RC-H and hydrolyses are in general acid- and/or base-catalyzed processes (Isaacs, 1987a; Reist et al., 1995) and thus expected to be pH-dependent. Also, both processes are thought to proceed faster in aqueous than in methanolic solutions (Isaacs, 1987b). Both reaction rates were also found to be proportional to the phosphate concentration. With a 3-fold increase in phosphate concentration, the rate constant of chiral inversion increased 1.1-fold and that of hydrolysis 1.3-fold. Hence, chiral inversion and hydrolysis of clopidogrel followed a very weak general-base catalysis, in contrast to the marked general-base catalysis seen in cases of ready racemization (Reist et al., 1995, 1996). Because the rates of chiral inversion and hydrolysis decreased only very slowly with increasing ionic strength, it can be deduced that phosphate concentration and ionic strength have only a marginal influence on the chiral inversion and hydrolysis of clopidogrel.

Although the nonenzymatic chiral inversion of the (S)-acid is improbable, due to the fact that a carboxy group is known to stabilize chiral carbon atoms of the type R’R’/RC-H (Testa et al., 1993; Reist et al., 1997), its configurational stability was investigated by \(^1\)H NMR. \(^1\)H NMR has previously been shown to be a suitable tool to assay inversion of chiral centers of the type R’R’/RC-H (Kawazoe and Ohnishi, 1964; Testa, 1973; Reist et al., 1995, 1996). The method takes advantage of the fact that the inversion of such chiral centers and proton-deuterium exchange share a common mechanism. As expected, no deuteration was observed and the configuration of (S)-acid was found to be stable up to 45 days in all media studied.

Enzymatic chiral inversion of clopidogrel and its carboxylic acid
derivatives was investigated in rat hepatocyte suspensions. In contrast to nonenzymatic chiral inversion, which is of ubiquitous occurrence, only a limited variety of enzymatic reactions are known to interconvert stereoisomers (Testa et al., 1993). One of them is the enzymatic chiral inversion of anti-inflammatory 2-arylpropionic acids (Knhi

icki et al., 1989; Mayer, 1990). The inactive (R)-enantiomer of ibuprofen and a few analogues are enantioselectively conjugated with coenzyme A to yield the (R)-acyl-CoA thioester. This conjugate is then epimerized to a mixture of the (S)- and (R)-acyl-CoA, followed by hydrolysis to yield a proen enriched in the (S)-form. Because this reaction was observed in isolated rat hepatocyte suspensions (Mayer et al., 1994; Roy-de Vos et al., 1996), the same investigation medium was chosen to study the possibility that the clopidogrel acids invert via a similar reaction mechanism. However, our results show that neither clopidogrel nor its carboxylic acid derivatives were subject to enzymatic chiral inversion in rat hepatocyte suspensions. Indeed, when clopidogrel was incubated, only the (S)-acid was formed, and when either (S)- or (R)-acid were incubated, no formation of the corresponding antipode could be observed.

In summary, the apparent rate constants of nonenzymatic chiral inversion of clopidogrel at 37°C in phosphate buffers, the absence of nonenzymatic chiral inversion of (S)-acid, and the lack of enzymatic chiral inversion of clopidogrel and its carboxylic acid derivatives in rat hepatocyte suspensions seem to be in good agreement with the 4 to 8% of chiral inversion seen in rats. From our results we deduce that nonenzymatic inversion of the ester, even if slow in the investigated media, accounts for the 4 to 8% of chiral inversion occurring in vivo in rats. To confirm our hypothesis, additional experiments conducted in protein solution and plasma could be of interest. Indeed, endogeneous bases such as proteins, amines and amino acids, thiolate groups, and carbonate can be expected to contribute to an acceleration of the nonenzymatic chiral inversion (Reist et al., 1995). In humans, plasma levels of the (R)-acid were consistently below the limit of detection (Necciari et al., 1996) after single oral administration of clopidogrel doses up to 150 mg.

In conclusion, the nonenzymatic inversion of clopidogrel demonstrated in vivo in rats during preclinical development has no clinical significance.

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References


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