

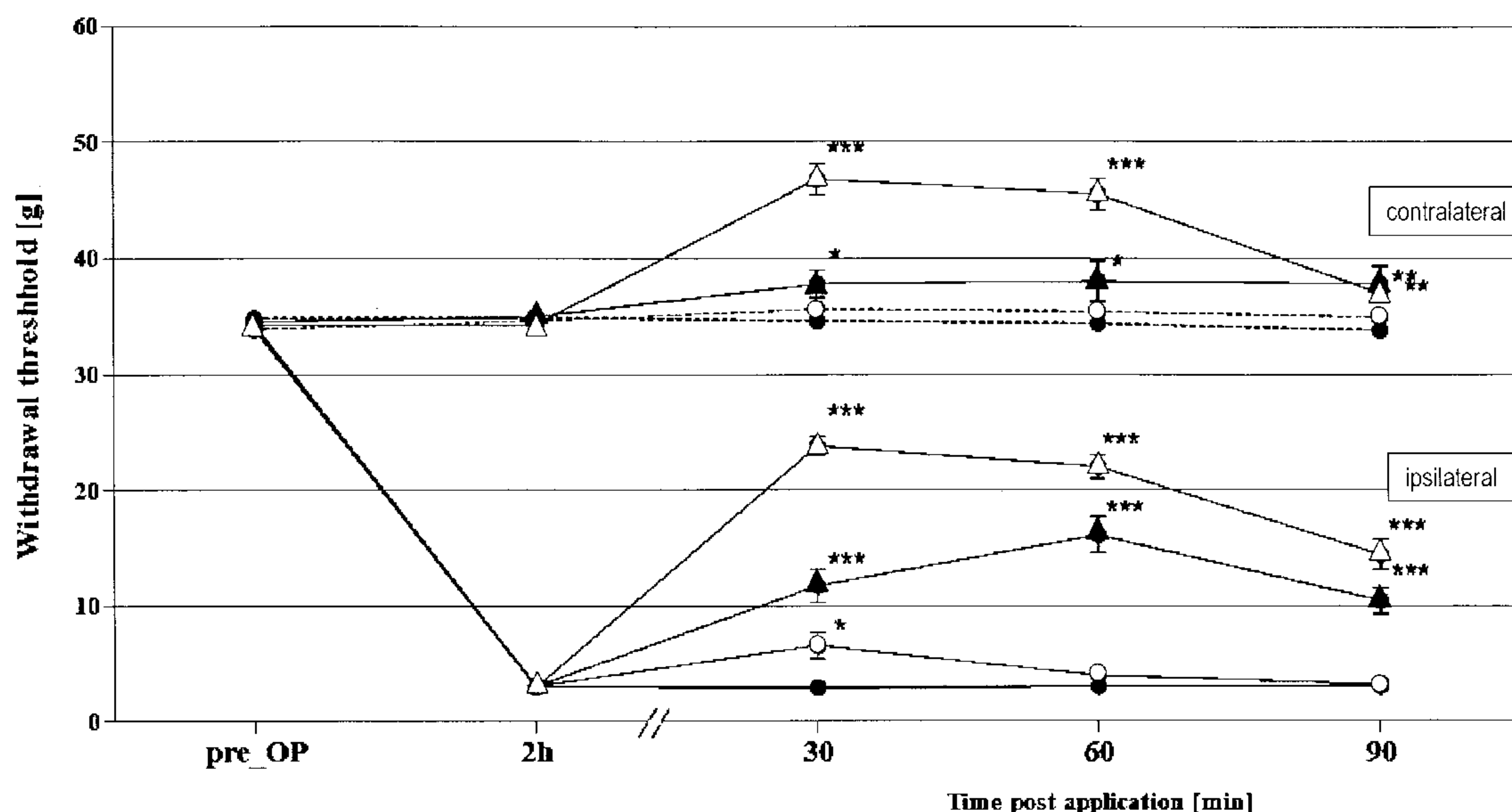


(86) Date de dépôt PCT/PCT Filing Date: 2013/05/16
(87) Date publication PCT/PCT Publication Date: 2013/11/21
(85) Entrée phase nationale/National Entry: 2014/11/14
(86) N° demande PCT/PCT Application No.: EP 2013/001470
(87) N° publication PCT/PCT Publication No.: 2013/170971
(30) Priorité/Priority: 2012/05/18 (EP12003895.5)

(51) Cl.Int./Int.Cl. *A61K 31/407* (2006.01),
A61K 31/196 (2006.01), *A61K 31/405* (2006.01),
A61K 45/06 (2006.01), *A61P 19/00* (2006.01),
A61P 25/00 (2006.01), *A61P 29/00* (2006.01)
(71) Demandeur/Applicant:
GRUNENTHAL GMBH, DE
(72) Inventeurs/Inventors:
FROSCH, STEFANIE, DE;
LINZ, KLAUS, DE;
SCHIENE, KLAUS, DE
(74) Agent: FETHERSTONHAUGH & CO.

(54) Titre : COMPOSITION PHARMACEUTIQUE COMPRENANT DE LA (1R,4R)-6'-FLUORO-N,N-DIMETHYL-4-PHENYL-4',9'-DIHYDRO-3'H-SPIRO[CYCLOHEXANE-1,1'-PYRANO[3,4,B]INDOL]-4-AMINE ET UN ARNS
(54) Title: PHARMACEUTICAL COMPOSITION COMPRISING (1R,4R)-6'-FLUORO-N,N-DIMETHYL-4-PHENYL-4',9'-DIHYDRO-3'H-SPIRO[CYCLOHEXANE-1,1'-PYRANO[3,4,B]INDOL]-4-AMINE AND A NSAR

Figure 1



(57) Abrégé/Abstract:

The invention relates to a pharmaceutical composition comprising a first pharmacologically active ingredient selected from (1r,4r)-6'-fluoro-N,N-dimethyl-4-phenyl-4',9'-dihydro-3'H-spiro[cyclohexane-1,1'-pyrano[3,4,b]indol]-4-amine and the physiologically acceptable salts thereof, and a second pharmacologically active ingredient which is a non-steroidal antirheumatic drug selected from the group consisting of indometacin, diclofenac, sulindac, tolmetin, zomepirac, aclofenac, bumadizone, etodolac, lonazolac, fentiazac, acemetacin, difenpiramide, oxametacin, proglumetacin, ketorolac, aceclofenac, bufexamac, mefenamic acid, tolfenamic acid, flufenamic acid, meclofenamic acid, and the physiologically acceptable salts thereof.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau(43) International Publication Date
21 November 2013 (21.11.2013)

WIPO | PCT

(10) International Publication Number
WO 2013/170971 A1

(51) International Patent Classification:

A61K 31/407 (2006.01) A61P 29/00 (2006.01)
A61K 31/196 (2006.01) A61P 19/00 (2006.01)
A61K 31/405 (2006.01) A61P 25/00 (2006.01)
A61K 45/06 (2006.01)

(21) International Application Number:

PCT/EP2013/001470

(22) International Filing Date:

16 May 2013 (16.05.2013)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

12003895.5 18 May 2012 (18.05.2012) EP

(71) Applicant: GRÜNENTHAL GMBH [DE/DE]; GI-I Pat-
ents, Zieglerstrasse 6, 52078 Aachen (DE).(72) Inventors: FROSCH, Stefanie; Beckerstrasse 49, 52078
Aachen (DE). LINZ, Klaus; Nachtigallengrund 5, 53359
Rheinbach (DE). SCHIENE, Klaus; Schaan 51, 41363
Jüchen (DE).(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,
AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY,

BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM,
DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT,
HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP,
KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD,
ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI,
NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU,
RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ,
TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA,
ZM, ZW.

(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ,
UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ,
TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK,
EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV,
MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM,
TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,
ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

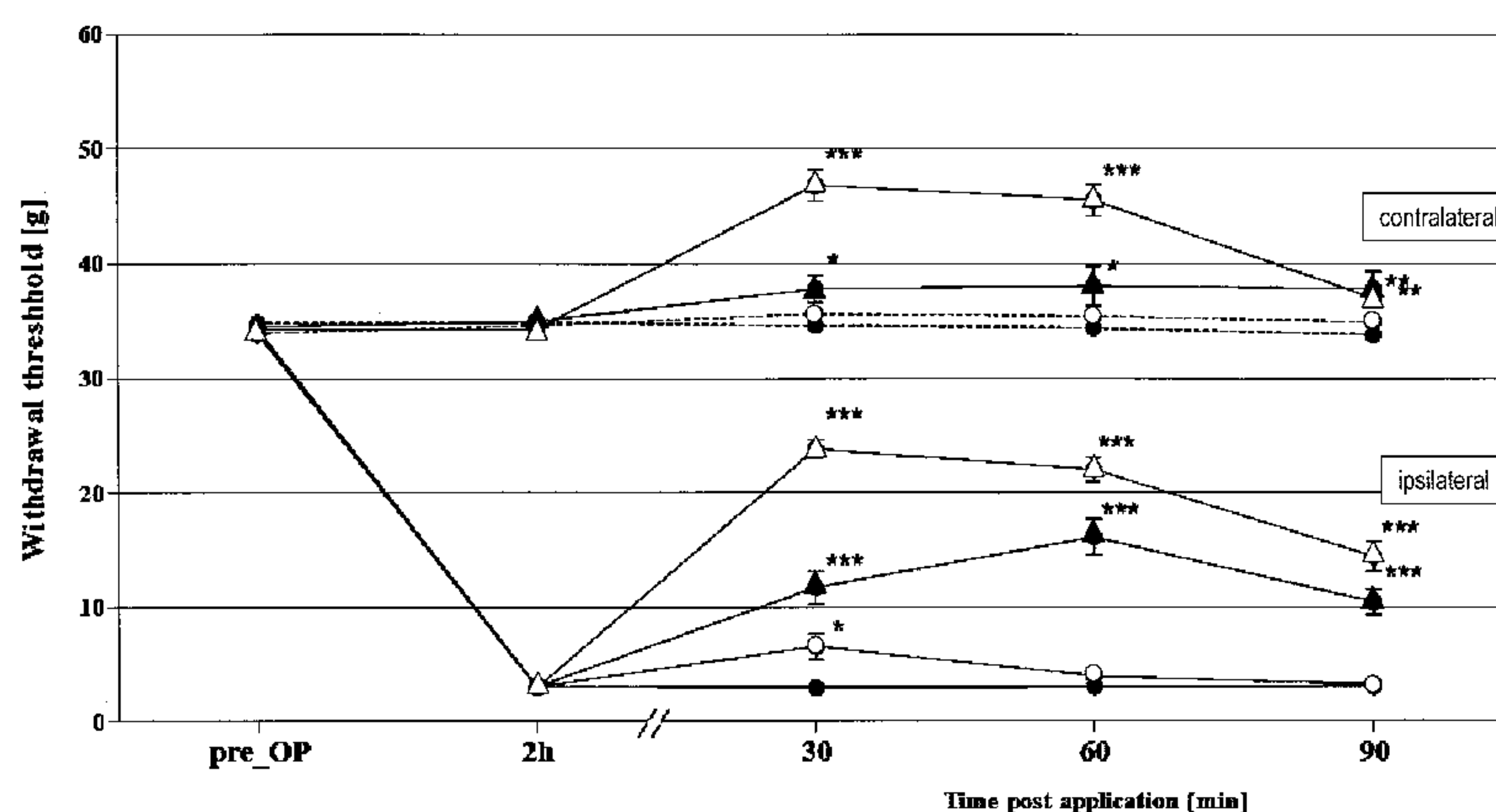
— as to applicant's entitlement to apply for and be granted a
patent (Rule 4.17(ii))

Published:

— with international search report (Art. 21(3))

(54) Title: PHARMACEUTICAL COMPOSITION COMPRISING (1R,4R)-6'-FLUORO-N,N-DIMETHYL-4-PHENYL-4',9'-DI-
HYDRO-3'H-SPIRO[CYCLOHEXANE-1,1'-PYRANO [3,4,B]INDOL]-4-AMINE AND A NSAR

Figure 1



(57) Abstract: The invention relates to a pharmaceutical composition comprising a first pharmacologically active ingredient selected from (1r,4r)-6'-fluoro-N,N-dimethyl-4-phenyl-4',9'-dihydro-3'H-spiro[cyclohexane-1,1'-pyrano[3,4,b]indol]-4-amine and the physiologically acceptable salts thereof, and a second pharmacologically active ingredient which is a non-steroidal antirheumatic drug selected from the group consisting of indometacin, diclofenac, sulindac, tolmetin, zomepirac, aclofenac, bumadizone, etodolac, lonazolac, fentiazac, acemetacin, difenpiramide, oxametacin, proglumetacin, ketorolac, aceclofenac, bufexamac, mefenamic acid, tolfenamic acid, flufenamic acid, meclofenamic acid, and the physiologically acceptable salts thereof.

WO 2013/170971 A1

Pharmaceutical composition comprising (1r,4r)-6'-fluoro-N,N-dimethyl-4-phenyl-4',9'-dihydro-3'H-spiro[cyclohexane-1,1'-pyrano[3,4,b]indol]-4-amine and a NSAR

The invention relates to a pharmaceutical composition comprising a first pharmacologically active ingredient selected from (1r,4r)-6'-fluoro-N,N-dimethyl-4-phenyl-4',9'-dihydro-3'H-spiro[cyclohexane-1,1'-pyrano[3,4,b]indol]-4-amine and the physiologically acceptable salts thereof, and a second pharmacologically active ingredient which is a non-steroidal anti-rheumatic drug (NSAR) selected from the group consisting of indometacin, diclofenac, sulindac, tolmetin, zomepirac, aclofenac, bumadizone, etodolac, lonazolac, fentiazac, acetaminophen, difenpiramide, oxametacin, proglumetacin, ketorolac, aceclofenac, bufexamac, mefenamic acid, tolfenamic acid, flufenamic acid, meclofenamic acid, and the physiologically acceptable salts thereof.

(1r,4r)-6'-fluoro-N,N-dimethyl-4-phenyl-4',9'-dihydro-3'H-spiro[cyclohexane-1,1'-pyrano[3,4,b]indol]-4-amine and its corresponding physiologically acceptable salts as well as methods for their preparation are well known, for example, from WO2004/043967 and WO2008/040481. The compounds exhibit analgesic properties and are particularly suitable for the treatment of acute, visceral, neuropathic or chronic (nociceptive) pain.

Non-steroidal anti-rheumatic drugs (NSARs), such as diclofenac and indometacin, are widely used for treating various pain conditions.

Though both of the aforementioned substance classes can be used in the prevention and treatment of pain and are as such therapeutically effective, side effects may occur, especially upon prolonged use or when administered at high dosages.

It is further known that specific combinations of pharmacologically active compounds exert supra-additive (synergistic) therapeutic effects upon administration. An advantage of these special cases is that the overall dose and accordingly the risk of undesired side effects may be reduced.

In a further aspect, two pharmacologically active compounds exerting a synergistic effect may be combined in one single pharmaceutical dosage form, e.g. a tablet, thus enhancing patient compliance.

It is an object of the invention to provide pharmaceutical compositions which have advantages compared to pharmaceutical compositions of the prior art. In particular, the pharmaceutical compositions should provide rapid therapeutic effects, but also should have a high tolerability, good compliance and safety.

This object has been achieved by the subject-matter of the patent claims.

It has been surprisingly found that a pharmaceutical composition comprising (1r,4r)-6'-fluoro-N,N-dimethyl-4-phenyl-4',9'-dihydro-3'H-spiro[cyclohexane-1,1'-pyrano[3,4,b]indol]-4-amine and a NSAR, such as indometacin and diclofenac, is useful for the treatment of acute and chronic pain.

Further it has been surprisingly found that said pharmaceutical composition exhibits a synergistic therapeutic effect upon administration. Therefore, the overall administered dose may be lowered, so that fewer undesired side-effects will occur.

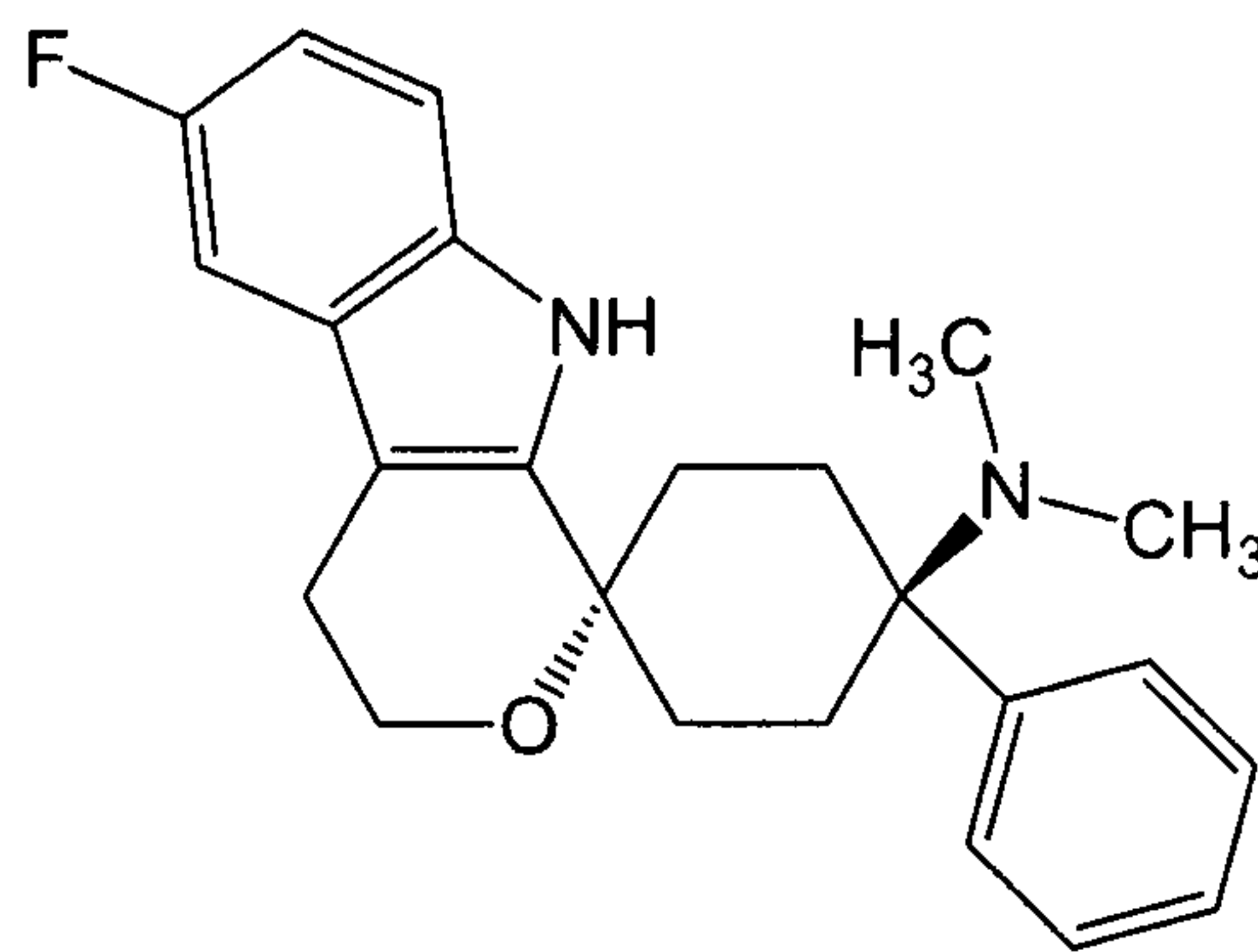
A first aspect of the invention relates to a pharmaceutical composition comprising:

- (a) a first pharmacologically active ingredient selected from (1r,4r)-6'-fluoro-N,N-dimethyl-4-phenyl-4',9'-dihydro-3'H-spiro[cyclohexane-1,1'-pyrano[3,4,b]indol]-4-amine and the physiologically acceptable salts thereof, and
- (b) a second pharmacologically active ingredient which is a non-steroidal anti-rheumatic drug selected from the group consisting of indometacin, diclofenac, sulindac, tolmetin, zomepirac, aclofenac, bumadizone, etodolac, lonazolac, fentiazac, acemetacin, difenpiramide, oxametacin, proglumetacin, ketorolac, aceclofenac, bufexamac, mefenamic acid, tolfenamic acid, flufenamic acid, meclofenamic acid, and the physiologically acceptable salts thereof.

The pharmaceutical composition according to the invention comprises a first pharmacologically active ingredient selected from (1r,4r)-6'-fluoro-N,N-dimethyl-4-phenyl-4',9'-dihydro-3'H-spiro[cyclohexane-1,1'-pyrano[3,4,b]indol]-4-amine and the physiologically acceptable salts thereof.

For the purpose of specification, (1r,4r)-6'-fluoro-N,N-dimethyl-4-phenyl-4',9'-dihydro-3'H-spiro[cyclohexane-1,1'-pyrano [3,4,b]indol]-4-amine is the compound according to formula (I)

which can also be referred to as 1,1-(3-dimethylamino-3-phenylpentamethylene)-6-fluoro-1,3,4,9-tetrahydropyrano[3,4-b]indole (trans)



(I).

The definition of the first pharmacologically active ingredient includes (1r,4r)-6'-fluoro-N,N-dimethyl-4-phenyl-4',9'-dihydro-3'H-spiro[cyclohexane-1,1'-pyrano-[3,4,b]indol]-4-amine in form of the free base, i.e. the compound according to formula (I), in any possible form including solvates, cocrystals and polymorphs, and its physiologically acceptable salts, in particular acid addition salts and corresponding solvates, cocrystals and polymorphs.

The pharmacologically active ingredient (1r,4r)-6'-fluoro-N,N-dimethyl-4-phenyl-4',9'-dihydro-3'H-spiro[cyclohexane-1,1'-pyrano[3,4,b]indol]-4-amine may be present in the pharmaceutical composition according to the invention in form of a physiologically acceptable salt, preferably an acid addition salt, whereby any suitable acid capable of forming such an addition salt may be used.

The conversion of (1r,4r)-6'-fluoro-N,N-dimethyl-4-phenyl-4',9'-dihydro-3'H-spiro[cyclohexane-1,1'-pyrano[3,4,b]indol]-4-amine into a corresponding addition salt, for example, via reaction with a suitable acid may be effected in a manner well known to those skilled in the art. Suitable acids include but are not limited to hydrochloric acid, hydrobromic acid, sulfuric acid, methanesulfonic acid, formic acid, acetic acid, oxalic acid, succinic acid, tartaric acid, mandelic acid, fumaric acid, lactic acid, citric acid, glutamic acid and/or aspartic acid. Salt formation is preferably effected in a solvent, for example, diethyl ether, diisopropyl ether, alkyl acetates, acetone and/or 2-butanone. Moreover, trimethylchlorosilane in aqueous solution is also suitable for the preparation of hydrochlorides.

In a preferred embodiment, the first pharmacologically active ingredient is (1r,4r)-6'-fluoro-N,N-dimethyl-4-phenyl-4',9'-dihydro-3'H-spiro[cyclohexane-1,1'-pyrano[3,4,b]indol]-4-amine in form of the free base, i.e. the compound according to formula (I).

In another preferred embodiment, the first pharmacologically active ingredient is (1r,4r)-6'-fluoro-N,N-dimethyl-4-phenyl-4',9'-dihydro-3'H-spiro[cyclohexane-1,1'-pyrano[3,4,b]indol]-4-amine in form of a physiologically acceptable acid addition salt, in particular the hydrochloride, hemicitrate or maleate salt.

Unless explicitly stated otherwise, all amounts of the first pharmacologically active ingredient specified in the following are given according to the corresponding amount of (1r,4r)-6'-fluoro-N,N-dimethyl-4-phenyl-4',9'-dihydro-3'H-spiro[cyclohexane-1,1'-pyrano[3,4,b]indol]-4-amine in form of the free base, i.e. the compound according to formula (I).

The pharmaceutical composition according to the invention comprises a second pharmacologically active ingredient which is a non-steroidal anti-rheumatic drug (NSAR) selected from the group consisting of indometacin, diclofenac, sulindac, tolmetin, zomepirac, aclofenac, bumadizone, etodolac, lonazolac, fentiazac, acemetacin, difenpiramide, oxametacin, proglumetacin, ketorolac, aceclofenac, bufexamac, mefenamic acid, tolfenamic acid, flufenamic acid, meclofenamic acid, and the physiologically acceptable salts thereof.

The definition of the second pharmacologically active ingredient includes the aforementioned NSARs in any possible form including any enantiomers, if applicable, solvates, prodrugs, cocrystals and polymorphs, and their physiologically acceptable salts, in particular metal salts and corresponding solvates, cocrystals and polymorphs.

The compounds indometacin, diclofenac, sulindac, tolmetin, zomepirac, aclofenac, bumadizone, etodolac, lonazolac, fentiazac, acemetacin, difenpiramide, oxametacin, proglumetacin, ketorolac, aceclofenac, bufexamac, mefenamic acid, tolfenamic acid, flufenamic acid and meclofenamic acid are carboxylic acids and thus, may each be converted into a corresponding metal salt in a manner well known to those skilled in the art, for example, via reaction with a suitable base as well as metal salt. Suitable bases include but are not limited to inorganic bases, including the hydroxides of sodium, potassium, calcium, magnesium, aluminium and zinc; and organic bases, such as triethyl amine, trimethylamine, N,N-diisopropylethylamine, N-methylmorpholine, morpholine, N-methylpiperidine, imidazole and ammonia. Suitable metal salts include but are not limited to alkali salts such as sodium, potassium or lithium phosphate, sulfate, methanesulfonate, formate, acetate, oxalate, succinate, tartrate, mandelate, fumarate, lactate, citrate, glutamate, aspartate and/or silyls, as well as alkaline earth salts, in particular magnesium and calcium salts, including their phosphate, sulfate, methanesulfonate, formate, acetate,

oxalate, succinate, tartrate, mandelate, fumarate, lactate, citrate, glutamate, aspartate and/or silyl salts. Salt formation is preferably effected in a solvent, for example, diethyl ether, diisopropyl ether, alkyl acetates, acetone and/or 2-butanone.

As prodrugs of NSARs, amides and esters are particularly preferred. Suitable methods for selecting and preparing a prodrug of a given substance are, for example, described in "Textbook of Drug Design and Discovery, 3rd edition, 2002, chapter 14, pages 410-458, Editors: Krogsgaard-Larsen et al., Taylor and Francis.

In a preferred embodiment, the second pharmacologically active ingredient is a NSAR selected from the group consisting of indometacin, diclofenac, sulindac, tolmetin, zomepirac, aclofenac, bumadizone, etodolac, lonazolac, fentiazac, acemetacin, difenpiramide, oxametacin, proglumetacin, ketorolac, aceclofenac, bufexamac, and the physiologically acceptable salts thereof.

In another preferred embodiment, the second pharmacologically active ingredient is a NSAR selected from the group consisting of mefenamic acid, tolfenamic acid, flufenamic acid, meclofenamic acid, and the physiologically acceptable salts thereof.

In a preferred embodiment, the second pharmacologically active ingredient is selected from the group consisting of indometacin, diclofenac, and the physiologically acceptable salts thereof, in particular the calcium, magnesium, sodium and potassium salts thereof.

Unless explicitly stated otherwise, all amounts of the second pharmacologically active ingredient specified in the following are given according to the corresponding amount of the free carboxylic acid.

In a preferred embodiment, the second pharmacologically active ingredient is indometacin or diclofenac.

In another preferred embodiment, the second pharmacologically active ingredient is selected from the metal salts of indometacin and diclofenac, in particular the calcium, magnesium, sodium and potassium salts thereof.

In an especially preferred embodiment, the second pharmacologically active ingredient is selected from indometacin, indometacin sodium, diclofenac potassium and diclofenac sodium.

In a preferred embodiment, the first pharmacologically active ingredient is (1r,4r)-6'-fluoro-N,N-dimethyl-4-phenyl-4',9'-dihydro-3'H-spiro[cyclohexane-1,1'-pyrano[3,4,b]indol]-4-amine in form of the free base, i.e. the compound according to formula (I), and the second pharmacologically active ingredient is selected from the group consisting of indometacin, diclofenac, and the physiologically acceptable salts thereof, in particular the calcium, magnesium, sodium and potassium salts thereof.

In another preferred embodiment, the first pharmacologically active ingredient is (1r,4r)-6'-fluoro-N,N-dimethyl-4-phenyl-4',9'-dihydro-3'H-spiro[cyclohexane-1,1'-pyrano[3,4,b]indol]-4-amine in form of a physiologically acceptable acid addition salt, in particular the hydrochloride, hemicitrate or maleate salt, and the second pharmacologically active ingredient is selected from the group consisting of indometacin, diclofenac, and the physiologically acceptable salts thereof, in particular the calcium, magnesium, sodium and potassium salts thereof.

In a preferred embodiment, the first pharmacologically active ingredient is (1r,4r)-6'-fluoro-N,N-dimethyl-4-phenyl-4',9'-dihydro-3'H-spiro[cyclohexane-1,1'-pyrano[3,4,b]indol]-4-amine in form of the free base, i.e. the compound according to formula (I), and the second pharmacologically active ingredient is selected from indometacin and diclofenac.

In another preferred embodiment, the first pharmacologically active ingredient is (1r,4r)-6'-fluoro-N,N-dimethyl-4-phenyl-4',9'-dihydro-3'H-spiro[cyclohexane-1,1'-pyrano[3,4,b]indol]-4-amine in form of the free base, i.e. the compound according to formula (I), and the second pharmacologically active ingredient is selected from the metal salts of indometacin and diclofenac, in particular the calcium, magnesium, sodium and potassium salts thereof.

In a further preferred embodiment, the first pharmacologically active ingredient is (1r,4r)-6'-fluoro-N,N-dimethyl-4-phenyl-4',9'-dihydro-3'H-spiro[cyclohexane-1,1'-pyrano[3,4,b]indol]-4-amine in form of a physiologically acceptable acid addition salt, in particular the hydrochloride, hemicitrate or maleate salt, and the second pharmacologically active ingredient is selected from indometacin and diclofenac.

In a still further preferred embodiment, the first pharmacologically active ingredient is (1r,4r)-6'-fluoro-N,N-dimethyl-4-phenyl-4',9'-dihydro-3'H-spiro[cyclohexane-1,1'-pyrano[3,4,b]indol]-4-amine in form of a physiologically acceptable acid addition salt, in particular the hydrochloride, hemicitrate or maleate salt, and the second pharmacologically active

ingredient is selected from the group consisting of indometacin, diclofenac, and the physiologically acceptable salts thereof, in particular the calcium, magnesium, sodium and potassium salts thereof.

Since the second pharmacologically active ingredient contains a carboxyl group, it may react with the first pharmacologically active ingredient according to formula (I) forming a salt which incorporates both pharmacologically active ingredients.

Thus, in another preferred embodiment, the pharmaceutical composition according to the invention comprises the first and the second pharmacologically active ingredient in form of a salt formed from these two pharmacologically active ingredients. Such a salt formation may be partial, i.e. the pharmaceutical composition according to the invention comprises one or both of these pharmacologically active ingredients also in their non-salt form, or the salt formation may essentially be complete.

Another aspect of the invention relates to a pharmaceutical dosage form comprising the pharmaceutical composition according to the invention.

The first and the second pharmacologically active ingredient are typically contained in the pharmaceutical dosage form according to the invention in a therapeutically effective amount. The amount that constitutes a therapeutically effective amount varies according to the pharmacologically active ingredients, the condition being treated, the severity of said condition, the patient being treated, and whether the pharmaceutical dosage form is designed for an immediate or controlled release.

In a preferred embodiment, the content of the first pharmacologically active ingredient in the pharmaceutical dosage form according to the invention and the pharmaceutical composition according to the invention, respectively, is at most 10 wt.-% or at most 5 wt.-% or at most 3 wt.-% or at most 1.0 wt.-%, more preferably at most 0.8 wt.-%, yet more preferably at most 0.5 wt.-%, still more preferably at most 0.2 wt.-%, even more preferably at most 0.1 wt.-%, most preferably at most 0.05 wt.-%, and in particular at most 0.01 wt.-% or at most 0.005 wt.-% or at most 0.001 wt.-%.

In a preferred embodiment, the content of the second pharmacologically active ingredient in the pharmaceutical dosage form according to the invention and the pharmaceutical composition according to the invention, respectively, is at most 95 wt.-%, more preferably at most 80 wt.-%, yet more preferably at most 70 wt.-%, still more preferably at most 60 wt.-%,

even more preferably at most 55 wt.-%, most preferably at most 50 wt.-%, and in particular at most 45 wt.-%.

In a preferred embodiment, the content of the first pharmacologically active ingredient in the pharmaceutical dosage form according to the invention and the pharmaceutical composition according to the invention, respectively, is at least 0.0001 wt.-%, more preferably at least 0.0003 wt.-%, yet more preferably at least 0.0005 wt.-%, still more preferably at least 0.0008 wt.-%, even more preferably at least 0.001 wt.-%, most preferably at least 0.003 wt.-%, and in particular at least 0.005 wt.-%.

In a preferred embodiment, the content of the second pharmacologically active ingredient in the pharmaceutical dosage form according to the invention and the pharmaceutical composition according to the invention, respectively, is at least 0.1 wt.-%, more preferably at least 0.5 wt.-%, yet more preferably at least 1 wt.-%, still more preferably at least 3 wt.-%, even more preferably at least 5 wt.-%, most preferably at least 7.5 wt.-%, and in particular at least 10 wt.-%.

Unless explicitly stated otherwise, in the meaning of the invention the indication "wt.-%" shall mean weight of the respective ingredient per total weight of the pharmaceutical dosage form or per total weight of the pharmaceutical composition, respectively.

Preferably, in the pharmaceutical dosage form according to the invention and the pharmaceutical composition according to the invention, respectively, the relative weight ratio of the first pharmacologically active ingredient to the second pharmacologically active ingredient is within the range of from 1 : 2 to 1 : 1,000,000, more preferably 1 : 5 to 1 : 500,000, most preferably 1 : 10 to 1 : 100,000, and in particular 1 : 10 to 1 : 50,000.

In a preferred embodiment, in the pharmaceutical dosage form according to the invention and the pharmaceutical composition according to the invention, respectively, the relative weight ratio of the first pharmacologically active ingredient to the second pharmacologically active ingredient is within the range of from 1 : 5 to 1 : 2,000, more preferably 1 : 5 to 1 : 1,500, still more preferably 1 : 10 to 1 : 1,000, most preferably 1 : 20 to 1 : 500, and in particular 1 : 50 to 1 : 250.

In another preferred embodiment, in the pharmaceutical dosage form according to the invention and the pharmaceutical composition according to the invention, respectively, the relative weight ratio of the first pharmacologically active ingredient to the second

pharmacologically active ingredient is within the range of from 1 : 100 to 1 : 10,000, more preferably 1 : 200 to 1 : 7,500, still more preferably 1 : 500 to 1 : 5,000, most preferably 1 : 750 to 1 : 2,500, and in particular 1 : 900 to 1 : 2,000.

In still another preferred embodiment, in the pharmaceutical dosage form according to the invention and the pharmaceutical composition according to the invention, respectively, the relative weight ratio of the first pharmacologically active ingredient to the second pharmacologically active ingredient is within the range of from 1 : 500 to 1 : 50,000, more preferably 1 : 1,000 to 1 : 20,000, still more preferably 1 : 2,000 to 1 : 10,000, most preferably 1 : 3,000 to 1 : 8,000, and in particular 1 : 4,000 to 1 : 6,000.

In yet another preferred embodiment, in the pharmaceutical dosage form according to the invention and the pharmaceutical composition according to the invention, respectively, the relative weight ratio of the first pharmacologically active ingredient to the second pharmacologically active ingredient is within the range of from 1 : 1,000 to 1 : 100,000, more preferably 1 : 2,000 to 1 : 80,000, still more preferably 1 : 4,000 to 1 : 50,000, yet more preferably 1 : 6,000 to 1 : 20,000, most preferably 1 : 8,000 to 1 : 15,000, and in particular 1 : 9,000 to 1 : 12,500.

In a further preferred embodiment, in the pharmaceutical dosage form according to the invention and the pharmaceutical composition according to the invention, respectively, the relative weight ratio of the first pharmacologically active ingredient to the second pharmacologically active ingredient is within the range of from 1 : 5,000 to 1 : 500,000, more preferably 1 : 10,000 to 1 : 400,000, still more preferably 1 : 20,000 to 1 : 300,000, most preferably 1 : 40,000 to 1 : 250,000, and in particular 1 : 50,000 to 1 : 200,000.

Preferably, in the pharmaceutical dosage form according to the invention and the pharmaceutical composition according to the invention, respectively, the relative molar ratio of the first pharmacologically active ingredient to the second pharmacologically active ingredient is within the range of from 1 : 2 to 1 : 1,000,000, more preferably 1 : 5 to 1 : 500,000, most preferably 1 : 10 to 1 : 100,000, and in particular 1 : 10 to 1 : 50,000.

In a preferred embodiment, in the pharmaceutical dosage form according to the invention and the pharmaceutical composition according to the invention, respectively, the relative molar ratio of the first pharmacologically active ingredient to the second pharmacologically active ingredient is within the range of from 1 : 5 to 1 : 2,000, more preferably 1 : 5 to 1 :

1,500, still more preferably 1 : 10 to 1 : 1,000, most preferably 1 : 20 to 1 : 500, and in particular 1 : 50 to 1 : 250.

In another preferred embodiment, in the pharmaceutical dosage form according to the invention and the pharmaceutical composition according to the invention, respectively, the relative molar ratio of the first pharmacologically active ingredient to the second pharmacologically active ingredient is within the range of from 1 : 100 to 1 : 10,000, more preferably 1 : 200 to 1 : 7,500, still more preferably 1 : 500 to 1 : 5,000, most preferably 1 : 750 to 1 : 2,500, and in particular 1 : 900 to 1 : 2,000.

In still another preferred embodiment, in the pharmaceutical dosage form according to the invention and the pharmaceutical composition according to the invention, respectively, the relative molar ratio of the first pharmacologically active ingredient to the second pharmacologically active ingredient is within the range of from 1 : 500 to 1 : 50,000, more preferably 1 : 1,000 to 1 : 20,000, still more preferably 1 : 2,000 to 1 : 10,000, most preferably 1 : 3,000 to 1 : 8,000, and in particular 1 : 4,000 to 1 : 6,000.

In yet another preferred embodiment, in the pharmaceutical dosage form according to the invention and the pharmaceutical composition according to the invention, respectively, the relative molar ratio of the first pharmacologically active ingredient to the second pharmacologically active ingredient is within the range of from 1 : 1,000 to 1 : 100,000, more preferably 1 : 2,000 to 1 : 80,000, still more preferably 1 : 4,000 to 1 : 50,000, yet more preferably 1 : 6,000 to 1 : 20,000, most preferably 1 : 8,000 to 1 : 15,000, and in particular 1 : 9,000 to 1 : 12,500.

In a further preferred embodiment, in the pharmaceutical dosage form according to the invention and the pharmaceutical composition according to the invention, respectively, the relative molar ratio of the first pharmacologically active ingredient to the second pharmacologically active ingredient is within the range of from 1 : 5,000 to 1 : 500,000, more preferably 1 : 10,000 to 1 : 400,000, still more preferably 1 : 20,000 to 1 : 300,000, most preferably 1 : 40,000 to 1 : 250,000, and in particular 1 : 50,000 to 1 : 200,000.

The amounts of the first and the second pharmacologically active ingredient contained in the pharmaceutical dosage form according to the invention may vary depending on different factors well known to those skilled in the art, for example, the weight of the patient, the route of administration, the severity of the illness and the like.

In general, both pharmacologically active ingredients contained in the pharmaceutical dosage form according to the invention may be administered in amounts up to their maximum daily dose, which is known to those skilled in the art. For example, as the second pharmacologically active ingredient, diclofenac may preferably be administered to a patient in a maximum daily dose of up to 150 mg, and indometacin may preferably be administered to a patient in a maximum daily dose of up to 200 mg.

When administered in the prescribed manner, e.g. once daily or twice daily, the pharmaceutical dosage form according to the invention and the pharmaceutical composition according to the invention, respectively, preferably contain the first and the second pharmacologically active ingredient, independently of one another, in an amount corresponding to 75 ± 15 wt.-%, 75 ± 10 wt.-%, 75 ± 5 wt.-%, 50 ± 15 wt.-%, 50 ± 10 wt.-%, 50 ± 5 wt.-%, 25 ± 15 wt.-%, 25 ± 10 wt.-% or 25 ± 5 wt.-% of the respective maximum daily dose of the first and the second pharmacologically active ingredient, respectively.

Preferably, the pharmaceutical dosage form according to the invention contains the first pharmacologically active ingredient in a dose of from 0.1 μ g to 5,000 μ g, more preferably, 0.1 μ g to 2,500 μ g, still more preferably 1.0 μ g to 1,000 μ g, yet more preferably 10 to 800 μ g, most preferably 15 μ g to 600 μ g, and in particular 20 μ g to 440 μ g.

In a preferred embodiment, the pharmaceutical dosage form according to the invention contains the first pharmacologically active ingredient in a dose within the range of 13 ± 12 μ g, more preferably 13 ± 10 μ g, still more preferably 13 ± 8 μ g, yet more preferably 13 ± 6 μ g, even more preferably 13 ± 5 μ g, most preferably 13 ± 4 μ g, and in particular 13 ± 3 μ g.

In another preferred embodiment, the pharmaceutical dosage form according to the invention contains the first pharmacologically active ingredient in a dose within the range of 20 ± 15 μ g, more preferably 20 ± 13 μ g, still more preferably 20 ± 12 μ g, yet more preferably 20 ± 10 μ g, even more preferably 20 ± 8 μ g, most preferably 20 ± 6 μ g, and in particular 20 ± 5 μ g.

In still another preferred embodiment, the pharmaceutical dosage form according to the invention contains the first pharmacologically active ingredient in a dose within the range of 40 ± 35 μ g, more preferably 40 ± 30 μ g, still more preferably 40 ± 25 μ g, yet more preferably 40 ± 20 μ g, even more preferably 40 ± 15 μ g, most preferably 40 ± 10 μ g, and in particular 40 ± 5 μ g.

In yet another preferred embodiment, the pharmaceutical dosage form according to the invention contains the first pharmacologically active ingredient in a dose within the range of 60 ± 50 μg , more preferably 60 ± 40 μg , still more preferably 60 ± 30 μg , yet more preferably 60 ± 20 μg , most preferably 60 ± 10 μg , and in particular 60 ± 5 μg .

In a further preferred embodiment, the pharmaceutical dosage form according to the invention contains the first pharmacologically active ingredient in a dose within the range of 80 ± 70 μg , more preferably 80 ± 60 μg , still more preferably 80 ± 50 μg , yet more preferably 80 ± 40 μg , even more preferably 80 ± 20 μg , most preferably 80 ± 10 μg , and in particular 80 ± 5 μg .

In still a further embodiment, the pharmaceutical dosage form according to the invention contains the first pharmacologically active ingredient in a dose within the range of 100 ± 90 μg , more preferably 100 ± 80 μg , still more preferably 100 ± 60 μg , yet more preferably 100 ± 40 μg , even more preferably 100 ± 20 μg , most preferably 100 ± 10 μg , and in particular 100 ± 5 μg .

In yet a further preferred embodiment, the pharmaceutical dosage form according to the invention contains the first pharmacologically active ingredient in a dose within the range of 120 ± 100 μg , more preferably 120 ± 80 μg , still more preferably 120 ± 60 μg , yet more preferably 120 ± 40 μg , even more preferably 120 ± 20 μg , most preferably 120 ± 10 μg , and in particular 120 ± 5 μg .

In another preferred embodiment, the pharmaceutical dosage form according to the invention contains the first pharmacologically active ingredient in a dose within the range of 150 ± 90 μg , more preferably 150 ± 80 μg , still more preferably 150 ± 60 μg , yet more preferably 150 ± 40 μg , even more preferably 150 ± 20 μg , most preferably 150 ± 10 μg , and in particular 150 ± 5 μg .

In still another preferred embodiment, the pharmaceutical dosage form according to the invention contains the first pharmacologically active ingredient in a dose within the range of 170 ± 130 μg , more preferably 170 ± 100 μg , still more preferably 170 ± 80 μg , yet more preferably 170 ± 60 μg , even more preferably 170 ± 40 μg , most preferably 170 ± 20 μg , and in particular 170 ± 10 μg .

In yet another preferred embodiment, the pharmaceutical dosage form according to the invention contains the first pharmacologically active ingredient in a dose within the range of 200 ± 175 μg , more preferably 200 ± 150 μg , still more preferably 200 ± 125 μg , yet more

preferably 200 ± 100 μg , even more preferably 200 ± 75 μg , most preferably 200 ± 50 μg , and in particular 200 ± 25 μg .

In a further preferred embodiment, the pharmaceutical dosage form according to the invention contains the first pharmacologically active ingredient in a dose within the range of 400 ± 350 μg , more preferably 400 ± 300 μg , still more preferably 400 ± 250 μg , yet more preferably 400 ± 200 μg , even more preferably 400 ± 150 μg , most preferably 400 ± 100 μg , and in particular 400 ± 50 μg .

In another preferred embodiment, the pharmaceutical dosage form according to the invention contains the first pharmacologically active ingredient in a dose within the range of 600 ± 400 μg , more preferably 600 ± 300 μg , still more preferably 600 ± 250 μg , yet more preferably 600 ± 200 μg , even more preferably 600 ± 150 μg , most preferably 600 ± 100 μg , and in particular 600 ± 50 μg .

In still another preferred embodiment, the pharmaceutical dosage form according to the invention contains the first pharmacologically active ingredient in a dose within the range of 800 ± 550 μg , more preferably 800 ± 400 μg , still more preferably 800 ± 350 μg , yet more preferably 800 ± 250 μg , even more preferably 800 ± 150 μg , most preferably 800 ± 100 μg , and in particular 800 ± 50 μg .

In yet another preferred embodiment, the pharmaceutical dosage form according to the invention contains the first pharmacologically active ingredient in a dose within the range of $1,000 \pm 800$ μg , more preferably $1,000 \pm 600$ μg , still more preferably $1,000 \pm 500$ μg , yet more preferably $1,000 \pm 300$ μg , even more preferably $1,000 \pm 200$ μg , most preferably $1,000 \pm 100$ μg , and in particular $1,000 \pm 50$ μg .

In a further preferred embodiment, the pharmaceutical dosage form according to the invention contains the first pharmacologically active ingredient in a dose within the range of $1,200 \pm 1,000$ μg , more preferably $1,200 \pm 800$ μg , still more preferably $1,200 \pm 600$ μg , yet more preferably $1,200 \pm 400$ μg , even more preferably $1,200 \pm 200$ μg , most preferably $1,200 \pm 100$ μg , and in particular $1,200 \pm 50$ μg .

Preferably, the pharmaceutical dosage form according to the invention contains the second pharmacologically active ingredient in a dose of from 3 mg to 2,000 mg, more preferably 5 mg to 1,500 mg, most preferably 7.5 mg to 1,200 mg, and in particular 10 to 1,000 mg.

In a preferred embodiment, the pharmaceutical dosage form according to the invention contains the second pharmacologically active ingredient in a dose within the range of 25 ± 22 mg, more preferably 25 ± 20 mg, still more preferably 25 ± 15 mg, yet more preferably 25 ± 12 mg, even more preferably 25 ± 10 mg, most preferably 25 ± 7 mg, and in particular 25 ± 5 mg.

In another preferred embodiment, the pharmaceutical dosage form according to the invention contains the second pharmacologically active ingredient in a dose within the range of 50 ± 45 mg, more preferably 50 ± 40 mg, still more preferably 50 ± 30 mg, yet more preferably 50 ± 25 mg, even more preferably 50 ± 20 mg, most preferably 50 ± 15 mg, and in particular 50 ± 10 mg.

In still another preferred embodiment, the pharmaceutical dosage form according to the invention contains the second pharmacologically active ingredient in a dose within the range of 100 ± 90 mg, more preferably 100 ± 75 mg, still more preferably 100 ± 50 mg, yet more preferably 100 ± 40 mg, even more preferably 100 ± 30 mg, most preferably 100 ± 20 mg, and in particular 100 ± 10 mg.

In yet another preferred embodiment, the pharmaceutical dosage form according to the invention contains the second pharmacologically active ingredient in a dose within the range of 200 ± 150 mg, more preferably 200 ± 100 mg, still more preferably 200 ± 75 mg, yet more preferably 200 ± 50 mg, even more preferably 200 ± 35 mg, most preferably 200 ± 20 mg, and in particular 200 ± 10 mg.

In a further preferred embodiment, the pharmaceutical dosage form according to the invention contains the second pharmacologically active ingredient in a dose within the range of 500 ± 400 mg, more preferably 500 ± 300 mg, still more preferably 500 ± 200 mg, yet more preferably 500 ± 150 mg, even more preferably 500 ± 100 mg, most preferably 500 ± 75 mg, and in particular 500 ± 50 mg.

In a preferred embodiment, the pharmaceutical dosage form contains a NSAR selected from diclofenac, indometacin, and their physiologically acceptable salts as the second pharmacologically active ingredient in a dose within the range of 10 mg to 250 mg, more preferably in the range of 15 mg to 200 mg, even more preferably in the range of 20 mg to 150 mg, most preferably in the range of 35 mg to 125 mg, and in particular in the range of 50 mg to 150 mg.

In a preferred embodiment, the pharmaceutical dosage form contains diclofenac or a physiologically acceptable salt thereof as the second pharmacologically active ingredient in a

dose within the range of 10 mg to 250 mg, more preferably in the range of 15 mg to 200 mg, even more preferably in the range of 20 mg to 150 mg, most preferably in the range of 35 mg to 125 mg, and in particular in the range of 50 mg to 100 mg.

In another preferred embodiment, the pharmaceutical dosage form contains indometacin or a physiologically acceptable salt thereof as the second pharmacologically active ingredient in a dose within the range of 10 mg to 250 mg, more preferably in the range of 15 mg to 200 mg, even more preferably in the range of 20 mg to 150 mg, most preferably in the range of 35 mg to 125 mg, and in particular in the range of 50 mg to 150 mg.

In the pharmaceutical dosage form according to the invention, the dose of the first pharmacologically active ingredient is preferably within the range of from 1 : 20 to 20 : 1 of the amount which is equieffective to the dosage of the second pharmacologically active ingredient. In this regard, "equieffective" preferably means the dosage that would be required in order to achieve the equivalent desired therapeutic effect when being administered alone. A skilled person recognizes that when the desired therapeutic effect is an analgesic effect, the equieffective dosage is determined with respect to the analgesic properties of the first pharmacologically active ingredient and the second pharmacological ingredient.

For example, when the dose of the second pharmacologically active ingredient, which is contained in the pharmaceutical dosage form according to the invention, amounts to e.g. 30 mg and provides an analgesic effect E when being administered alone at this dose, and when the equieffective amount of the first pharmacologically active ingredient, i.e. the amount needed in order to provide the same analgesic effect E when being administered alone, would be e.g. 4 µg, the dosage of the first pharmacologically active ingredient, which is contained in the pharmaceutical dosage form according to the invention, may vary from 0.2 µg ($4 \mu\text{g}/20$) to 80 µg ($20 \cdot 4 \mu\text{g}$).

In a preferred embodiment, the dose of the first pharmacologically active ingredient is within the range of from 1 : 15 to 15 : 1, preferably within the range of from 1 : 10 to 10 : 1, more preferably within the range of from 1 : 8 to 8 : 1, still more preferably within the range of from 1 : 6 to 6 : 1, yet more preferably within the range of from 1 : 4 to 4 : 1, most preferably within the range of from 1 : 3 to 3 : 1, and in particular preferably within the range of from 1 : 2 to 2 : 1, of the amount which is equieffective to the dose of the second pharmacologically active ingredient.

Suitable pathways of administration of the pharmaceutical dosage form according to the invention include but are not limited to oral, intravenous, intraperitoneal, intradermal, transdermal, intrathecal, intramuscular, intranasal, transmucosal, subcutaneous, local and/or rectal administration.

In a preferred embodiment, the pharmaceutical dosage form according to the invention is for oral administration.

In another preferred embodiment, the pharmaceutical dosage form according to the invention is for parenteral administration, in particular intravenous, intraperitoneal, intrathecal, intramuscular, or subcutaneous administration.

In still another preferred embodiment, the pharmaceutical dosage form according to the invention is for rectal administration.

The pharmaceutical dosage form according to the invention and the pharmaceutical composition according to the invention, respectively, can be solid, semi-solid or liquid.

The pharmaceutical dosage form according to the invention and the pharmaceutical composition according to the invention, respectively, may contain auxiliary agents, for example, carriers, fillers, solvents, diluents, colorants and/or binders. The selection of auxiliary agents and of the amounts of the same to be used depends, for example, on how the first and the second pharmacologically active ingredient are to be administered, e.g. orally, intravenously, intraperitoneally, intradermally, transdermally, intrathecally, intramuscularly, intranasally, transmucosally, subcutaneously, rectally or locally.

Suitable auxiliary agents are in particular any substances known to a person skilled in the art useful for the preparation of galenical dosage forms. Examples of suitable auxiliary agents include but are not limited to: water, ethanol, 2-propanol, glycerol, ethylene glycol, propylene glycol, polyethylene glycol, polypropylene glycol, glucose, fructose, lactose, saccharose, dextrose, molasses, starch, modified starch, gelatine, sorbitol, inositol, mannitol, microcrystalline cellulose, methyl cellulose, carboxymethyl cellulose, cellulose acetate, shellac, cetyl alcohol, polyvinyl pyrrolidone, paraffins, waxes, natural and synthetic gums, acacia gum, alginates, dextran, saturated and unsaturated fatty acids, stearic acid, magnesium stearate, zinc stearate, glycerol stearate, sodium lauryl sulphate, edible oils, sesame oil, coconut oil, peanut oil, soybean oil, lecithin, sodium lactate, polyoxyethylene and polypropylene fatty acid ester, sorbitan fatty acid ester, sorbic acid, benzoic acid, citric acid,

ascorbic acid, tannic acid, sodium chloride, potassium chloride, magnesium chloride, calcium chloride, magnesium oxide, zinc oxide, silicon dioxide, titanium oxide, titanium dioxide, magnesium sulphate, zinc sulphate, calcium sulphate, potash, calcium phosphate, dicalcium phosphate, potassium bromide, potassium iodide, talcum, kaolin, pectin, crosspovidone, agar and bentonite.

Pharmaceutical dosage forms which are suitable for oral administration include but are not limited to tablets, effervescent tablets, chewing tablets, dragees, capsules, drops, juices and syrups. Oral pharmaceutical dosage forms may also be in the form of multiparticulates such as granules, pellets, spheres, crystals and the like, optionally compressed into a tablet, filled into a capsule, filled into a sachet or suspended in a suitable liquid medium. Oral pharmaceutical dosage forms may also be equipped with an enteric coating.

Pharmaceutical dosage forms that are suitable for parenteral, topical and inhalative administration include but are not limited to solutions, suspensions, easily reconstitutable dry preparations and sprays.

Suppositories are a suitable pharmaceutical dosage form for rectal administration. Dosage forms in a deposit, in dissolved form, for example, in a patch optionally with the addition of agents to promote skin penetration, are examples of suitable dosage forms for percutaneous administration.

In an especially preferred embodiment, the pharmaceutical dosage form according to the invention is a tablet.

In a preferred embodiment, the pharmaceutical dosage form according to the invention is for administration six times daily, five times daily, four times daily, thrice daily, twice daily, once daily, or less frequently.

In a preferred embodiment, the pharmaceutical dosage form according to the invention is preferably for administration once daily.

In another preferred embodiment, the pharmaceutical dosage form according to the invention is for administration multiple daily, in particular twice daily, thrice daily, or up to six times a day.

In a preferred embodiment, the pharmaceutical dosage form according to the invention is for administration twice daily.

In another preferred embodiment, the pharmaceutical dosage form according to the invention is for administration thrice daily.

For the purpose of specification, "administration thrice daily" (tid) preferably means that the pharmaceutical dosage form according to the invention is adapted for being consecutively administered according to a regimen comprising the administration of three pharmaceutical dosage forms per day, wherein the time interval between the consecutive administration of two pharmaceutical dosage forms is at least 3 hours, preferably at least 4 hours, more preferably not least 6 hours and in particular, about 8 hours.

For the purpose of specification, "administration twice daily" (bid) preferably means that the pharmaceutical dosage form according to the invention is adapted for being consecutively administered according to a regimen comprising the administration of two pharmaceutical dosage forms per day, wherein the time interval between the consecutive administration of two pharmaceutical dosage forms is at least 6 hours, preferably at least 8 hours, more preferably at least 10 hours and in particular, about 12 hours.

For the purpose of specification, "administration once daily" (sid) preferably means that the pharmaceutical dosage form according to the invention is adapted for being consecutively administered according to a regimen comprising the administration of one pharmaceutical dosage form per day, wherein the time interval between the consecutive administration of two pharmaceutical dosage forms is at least 18 hours, preferably at least 20 hours, more preferably at least 22 hours and in particular, about 24 hours.

A skilled person is fully aware that the above administration regimens may be realized by administering a single pharmaceutical dosage form containing the full amount of the first pharmacologically active ingredient and the full amount of the second pharmacologically active ingredient to be administered at a particular point in time or, alternatively, administering a multitude of dose units, i.e. two, three or more dose units, the sum of which multitude of dose units containing the full amount of the first pharmacologically active ingredient and the second pharmacologically active ingredient to be administered at said particular point in time, where the individual dose units are adapted for simultaneous administration or administration within a short period of time, e.g. within 5, 10 or 15 minutes.

In the following, the doses of the first and the second pharmacologically active ingredient are expressed according to the number of prescribed administrations "n" per day, i.e. the number of administrations of the pharmaceutical dosage form according to the invention in the course of 24 hours. As an example, $100/n$ μg in case of an administration once daily ($n = 1$) corresponds to a dose of 100 μg , and $100/n$ μg in case of an administration twice daily ($n = 2$) corresponds to a dose of 50 μg .

In a preferred embodiment, the pharmaceutical dosage form according to the invention is for administration once daily ($n = 1$), wherein the pharmaceutical dosage form contains the first pharmacologically active ingredient in a dose of from $15/n$ to $100/n$ μg , preferably $20/n$ to $80/n$ μg , and the second pharmacologically active ingredient in a dose of from $10/n$ to 1,000/n mg. According to this embodiment, the pharmaceutical dosage form according to the invention is preferably for oral administration, preferably in form of a tablet.

In another preferred embodiment, the pharmaceutical dosage form according to the invention is for administration multiple daily ($n = 2, 3, 4, 5$ or 6), wherein the pharmaceutical dosage form contains the first pharmacologically active ingredient in a dose of from $15/n$ to $100/n$ μg , preferably $20/n$ to $80/n$ μg , and the second pharmacologically active ingredient in a dose of from $10/n$ to 1,000/n mg. According to this embodiment, the pharmaceutical dosage form according to the invention is preferably for oral administration, preferably in form of a tablet. According to this embodiment, a twice daily or thrice daily administration can be especially preferred since the preferred doses of the second pharmacologically active ingredient may be as high as 1,000/n mg, thus rendering a tablet containing e.g. a maximum of 1,000/2 mg or 1,000/3 mg, respectively, of the second pharmacologically active ingredient much more patient compliant.

In still another preferred embodiment, the pharmaceutical dosage form according to the invention is for administration once daily ($n = 1$), wherein the pharmaceutical dosage form contains the first pharmacologically active ingredient in a dose of from $150/n$ to $1,200/n$ μg , preferably $200/n$ to $800/n$ μg , and the second pharmacologically active ingredient in a dose of from $10/n$ to 1,000/n mg. According to this embodiment, the pharmaceutical dosage form according to the invention is preferably for oral administration, preferably in form of a tablet.

In yet another preferred embodiment, the pharmaceutical dosage form according to the invention is for administration multiple daily ($n = 2, 3, 4, 5$ or 6), wherein the pharmaceutical dosage form contains the first pharmacologically active ingredient in a dose of from $150/n$ to $1,200/n$ μg , preferably $200/n$ to $800/n$ μg , and the second pharmacologically active ingredient

in a dose of from 10/n to 1,000/n mg. According to this embodiment, the pharmaceutical dosage form according to the invention is preferably for oral administration, preferably in form of a tablet. According to this embodiment, a twice daily or thrice daily administration can be especially preferred since the preferred doses of the second pharmacologically active ingredient may be as high as 1,000/n mg, thus rendering a tablet containing e.g. a maximum of 1,000/2 mg or 1,000/3 mg, respectively, of the second pharmacologically active ingredient much more patient compliant.

The pharmaceutical dosage form according to the invention may provide under *in vitro* conditions immediate release or controlled release of the first pharmacologically active ingredient and/or the second pharmacologically active ingredient. *In vitro* release is preferably determined in accordance with Ph. Eur., preferably paddle method with sinker, 75 rpm, 37 °C, 900 mL artificial gastric juice, pH 6.8.

The first pharmacologically active ingredient and/or the second pharmacologically active ingredient may independently of one another be present in the pharmaceutical dosage form at least partially in controlled-release form. For example, the first pharmacologically active ingredient and/or the second pharmacologically active ingredient may be released from the pharmaceutical dosage form in a prolonged manner, e.g. if administered orally, rectally or percutaneously. Such pharmaceutical dosage forms are particularly useful for "once-daily" or "twice-daily" preparations, which only have to be taken once a day, respectively, twice a day. Suitable controlled-release materials are well known to those skilled in the art.

The pharmaceutical dosage form according to the invention providing controlled release of the first pharmacologically active ingredient and/or the second pharmacologically active ingredient may be produced using materials, means, devices and processes that are well known in the prior art of pharmaceutical dosage forms.

In order to obtain a solid pharmaceutical dosage form such as a tablet, for example, the pharmacologically active ingredients of the pharmaceutical composition may be granulated with a pharmaceutical carrier, for example conventional tablet ingredients such as corn starch, lactose, saccharose, sorbitol, talcum, magnesium stearate, dicalcium phosphate or pharmaceutically acceptable gums, and pharmaceutical diluents, for example water, in order to form a solid composition that contains the pharmacologically active ingredients in homogeneous distribution. The term "homogeneous distribution" is taken to mean that the pharmacologically active ingredients are distributed uniformly over the entire composition, so that said composition may easily be divided into equally effective dose units, such as tablets,

pills or capsules and the like. The solid composition is then divided into dose units. The tablets or pills of the pharmaceutical composition according to the invention may also be coated or compounded in a different manner, in order to provide a dosage form with a controlled release.

If one of the pharmacologically active ingredients is to be released prior to the other pharmacologically active ingredient, for example at least 30 minutes or 1 hour beforehand, pharmaceutical dosage forms having a corresponding release profile may be prepared. An example of such a pharmaceutical dosage form is an osmotically-driven release system for achieving a delayed release of either the first or the second pharmacologically active ingredient from an inner part (core) of the pharmaceutical dosage form *via* a coating that itself contains the other pharmacologically active ingredient which is accordingly released earlier. In a release system of this kind, which is particularly suitable for oral administration, at least part, and preferably all, of the surface of the release system, preferably those parts that will come into contact with the release medium, is/are semipermeable, preferably equipped with a semipermeable coating, so the surface(s) is/are permeable to the release medium, but substantially, preferably entirely, impermeable to the pharmacologically active ingredient contained in the core, the surface(s) and/or optionally the coating comprising at least one opening for releasing the pharmacologically active ingredient contained in the core. Moreover, precisely that/those surface(s) that is/are in contact with the release medium is/are provided with a coating containing and releasing the other pharmacologically active ingredient. This is preferably taken to mean a system in tablet form comprising a release opening, a core containing the first or the second pharmacologically active ingredient, a polymer portion that exerts pressure upon swelling, a semipermeable membrane and a coating containing the other pharmacologically active ingredient. Embodiments and examples of osmotically-driven release systems are, for example, disclosed in US patents 4,765,989, 4,783,337 and 4,612,008.

A further example of a suitable pharmaceutical dosage form is a gel-matrix tablet. Suitable examples are provided in US patents 4,389,393, 5,330,761, 5,399,362, 5,472,711 and 5,455,046. Particularly suitable is a retarding matrix dosage form, with an inhomogeneous distribution of the pharmaceutical composition, whereby, for example, one pharmacologically active ingredient, i.e. the first or the second pharmacologically active ingredient, is distributed in the outer region (the portion that comes into contact with the release medium most quickly) of the matrix and the other pharmacologically active ingredient is distributed inside the matrix. On contact with the release medium, the outer matrix layer initially (and rapidly) swells and firstly releases the pharmacologically active ingredient contained therein, followed

by the significantly (more) controlled release of the other pharmacologically active ingredient. Examples of a suitable matrix include matrices with 1 to 80 % by weight of one or more hydrophilic or hydrophobic polymers as pharmaceutically acceptable matrix formers.

Preferably, the pharmaceutical dosage form according to the invention provides immediate release of the first pharmacologically active ingredient, and immediate or controlled release of the second pharmacologically active ingredient.

In a preferred embodiment, the pharmaceutical dosage form according to the invention provides immediate release of both, the first and the second pharmacologically active ingredient. In this particular case, a multiple daily administration, in particular an administration twice daily, thrice daily, or up to six times a day is preferred.

In another preferred embodiment, the pharmaceutical dosage form according to the invention provides immediate release of the first pharmacologically active ingredient, and controlled release of the second pharmacologically active ingredient. This release profile may be realized by employing the aforementioned methods, e.g. the osmotically-driven release system providing the first pharmacologically active ingredient in the coating and the second pharmacologically active ingredient in the core, or the retarding matrix dosage form containing the first pharmacologically active ingredient in the outer matrix layer and the second pharmacologically active ingredient in the inside of the matrix.

In yet another preferred embodiment, the pharmaceutical dosage form according to the invention provides controlled release of both the first and the second pharmacologically active ingredient.

In a further aspect, the invention relates to the use of the pharmaceutical composition according to the invention, and the pharmaceutical dosage form according to the invention respectively, in the prevention or treatment of pain.

In a preferred embodiment, the pharmaceutical composition according to the invention and the pharmaceutical dosage form according to the invention, respectively, are for use in the treatment of pain, wherein the pain is preferably

- peripheral, central or muscle skeletal pain; and/or
- acute, subacute or chronic pain; and/or
- moderate to severe pain; and/or
- neuropathic or psychogenic or nociceptive or mixed pain; and/or

- low back pain, visceral pain or headache; and/or
- post-operative (post-surgical), cancer or inflammatory pain.

For the purpose of specification, "acute pain" preferably refers to pain that lasts up to about 4 weeks, "subacute pain" preferably refers to pain that lasts from more than about 4 weeks to about 12 weeks, and "chronic pain" preferably refers to pain that lasts for more than about 12 weeks.

Preferably, the pain is selected from the group consisting of cancer pain, peripheral neuropathic pain, osteoarthritis, chronic visceral pain, neuropathic pain (diabetic polyneuropathy, HIV-associated neuropathic pain, posttraumatic neuropathic pain, postherpetic neuralgia, chemotherapy associated pain), postzosteric neuralgia, postoperative neuropathic pain, inflammatory pain, migraine, low-back pain, fibromyalgia and trigeminal neuralgia.

In a preferred embodiment, the pain is chronic pain, in particular chronic nociceptive pain and/or chronic inflammatory pain.

In another preferred embodiment, the pain is non-chronic or acute pain, in particular post-operative pain (post-surgical pain).

In a further preferred embodiment, the pain is selected from the group consisting of diabetic polyneuropathy, postzosteric neuralgia, postoperative neuropathic pain, low-back pain and fibromyalgia.

In the following, the doses of the first and the second pharmacologically active ingredient are again expressed according to the number of administrations "n" per day, i.e. the number of administrations of the pharmaceutical dosage form according to the invention in the course of 24 hours.

In a preferred embodiment, the pharmaceutical dosage form is for use in the treatment of neuropathic pain which may be optionally superimposed by nociceptive pain, where the dose of the first pharmacologically active ingredient contained in the pharmaceutical dosage form preferably is in the range of $1/n \mu\text{g}$ to $800/n \mu\text{g}$ or $1/n \mu\text{g}$ to $600/n \mu\text{g}$ or $1/n \mu\text{g}$ to $400/n \mu\text{g}$ or $1/n \mu\text{g}$ to $250/n \mu\text{g}$, more preferably in the range of $5/n \mu\text{g}$ to $150/n \mu\text{g}$, even more preferably in the range of $10/n \mu\text{g}$ to $100/n \mu\text{g}$, most preferably in the range of $20/n \mu\text{g}$ to $80/n \mu\text{g}$ and in particular most preferably in the range of $30/n \mu\text{g}$ to $50/n \mu\text{g}$. According to this embodiment,

the dose of the second pharmacologically active ingredient contained in the pharmaceutical dosage form preferably is in the range of 10/n mg to 1,000/n mg.

In a preferred embodiment, in particular when the pharmaceutical dosage form is for use in the treatment of neuropathic pain and the second pharmacologically active ingredient is selected from diclofenac, indometacin and their physiologically acceptable salts, the dose of the first pharmacologically active ingredient contained in the pharmaceutical dosage form preferably is in the range of 1/n μ g to 800/n μ g or 1/n μ g to 600/n μ g or 1/n μ g to 400/n μ g or 1/n μ g to 250/n μ g, more preferably in the range of 5/n μ g to 150/n μ g, even more preferably in the range of 10/n μ g to 100/n μ g, most preferably in the range of 20/n μ g to 80/n μ g and in particular most preferably in the range of 30/n μ g to 50/n μ g; and the dose of the second pharmacologically active ingredient contained in the pharmaceutical dosage form preferably is in the range of 10/n mg to 250/n mg, more preferably in the range of 15/n mg to 200/n mg, even more preferably in the range of 20/n mg to 150/n mg, most preferably in the range of 35/n mg to 125/n mg and in particular in the range of 50/n mg to 150/n mg.

In another preferred embodiment, the pharmaceutical dosage form is for use in the treatment of nociceptive pain which may be optionally superimposed by neuropathic pain, where the dose of the first pharmacologically active ingredient contained in the pharmaceutical dosage form preferably is in the range of 50/n μ g to 2,000/n μ g or 50/n μ g to 1,400/n μ g or 50/n μ g to 1,200/n μ g or 50/n μ g to 1,000/n μ g, more preferably in the range of 100/n μ g to 800/n μ g, still more preferably in the range of 150/n μ g to 650/n μ g, even more preferably in the range of 250/n μ g to 550/n μ g, and most preferably in the range of 350/n μ g to 450/n μ g. According to this embodiment, the dose of the second pharmacologically active ingredient contained in the pharmaceutical dosage form preferably is in the range of 10/n mg to 1,000/n mg.

In a preferred embodiment, in particular when the pharmaceutical dosage form is for use in the treatment of nociceptive pain and the second pharmacologically active ingredient is selected from diclofenac, indometacin and their physiologically acceptable salts, the dose of the first pharmacologically active ingredient contained in the pharmaceutical dosage form preferably is in the range of 50/n μ g to 2,000/n μ g or 50/n μ g to 1,400/n μ g or 50/n μ g to 1,200/n μ g or 50/n μ g to 1,000/n μ g, more preferably in the range of 100/n μ g to 800/n μ g, still more preferably in the range of 150/n μ g to 650/n μ g, even more preferably in the range of 250/n μ g to 550/n μ g, and most preferably in the range of 350/n μ g to 450/n μ g; and the dose of the second pharmacologically active ingredient contained in the pharmaceutical dosage form preferably is in the range of 10/n mg to 250/n mg, more preferably in the range of 15/n mg to 200/n mg, even more preferably in the range of 20/n mg to 150/n mg, most

preferably in the range of 35/n mg to 125/n mg and in particular in the range of 50/n mg to 150/n mg.

Preferably, the pharmaceutical composition contains the first and the second pharmacologically active ingredient in such a weight ratio that they will exert a synergistic therapeutic effect upon administration to a patient. Thereby, the term "synergistic therapeutic effect" may refer to a synergistic therapeutic effect with respect to the prevention or treatment of pain (synergistic analgesic effect), a synergistic therapeutic effect with respect to the prevention or treatment of anxiety (synergistic anxiolytic effect) as well as a synergistic therapeutic effect with respect to the prevention or treatment of epilepsy (synergistic anti-convulsive effect). Suitable weight ratios of the pharmacologically active ingredients generating the synergistic therapeutic effect can be determined by methods well known to those skilled in the art.

A further aspect of the invention relates to a method of treating or preventing pain comprising the preferably twice daily or once daily, preferably oral administration of the pharmaceutical dosage form according to the invention to a subject in need thereof.

In a particular preferred embodiment,

- the first pharmacologically active ingredient is (1r,4r)-6'-fluoro-N,N-dimethyl-4-phenyl-4',9'-dihydro-3'H-spiro[cyclohexane-1,1'-pyrano[3,4,b]indol]-4-amine according to formula (I) in form of its free base, or a hemicitrate, hydrochloride or maleate salt thereof; and/or
- the second pharmacologically active ingredient is selected from the group consisting of indometacin, diclofenac and the physiologically acceptable salts thereof; and/or
- the pharmaceutical composition and the pharmaceutical dosage form, respectively, contain the first pharmacologically active ingredient in a dose of from 20 µg to 80 µg or of from 80 µg to 200 µg or of from 200 µg to 800 µg or of from 800 µg to 1,200 µg; and/or
- the pharmaceutical composition and the pharmaceutical dosage form, respectively, contain the second pharmacologically active ingredient in a dose of from 10 mg to 250 mg; and/or
- the relative weight ratio of the first pharmacologically active ingredient to the second pharmacologically active ingredient is within the range of from 1 : 2 to 1 : 1,000,000,

preferably 1 : 10 to 1 : 50,000 in the pharmaceutical composition and the pharmaceutical dosage form, respectively; and/or

- the pharmaceutical composition is for use in the treatment of pain; wherein the pain is peripheral, central or muscle skeletal pain; and/or acute, subacute or chronic pain; and/or moderate to severe pain; and/or neuropathic or psychogenic or nociceptive or mixed pain; and/or low back pain, visceral pain or headache; and/or post-operative (post-surgical), cancer or inflammatory pain; and/or
- the pharmaceutical composition and the pharmaceutical dosage form, respectively, contain the first pharmacologically active ingredient and the second pharmacologically active ingredient in such a weight ratio that upon administration to a patient they will exert a synergistic therapeutic effect; and/or
- the pharmaceutical dosage form provides immediate release of the first pharmacologically active ingredient *in vitro* in accordance with Ph. Eur.; and/or
- the pharmaceutical dosage form provides immediate or controlled release of the second pharmacologically active ingredient *in vitro* in accordance with Ph. Eur.; and/or
- the pharmaceutical dosage form is for oral administration; and/or
- the pharmaceutical dosage form is for administration once, twice or thrice daily.

In a further aspect, the invention relates to a kit comprising a first pharmaceutical dosage form comprising the first pharmacologically active ingredient as described above, and a second pharmaceutical dosage form comprising the second pharmacologically active ingredient as described above.

A suitable embodiment is a kit in which the first pharmaceutical dosage form comprising the first pharmacologically active ingredient and the second pharmaceutical dosage form comprising the second pharmacologically active ingredient, although spatially separated, are provided in a common presentation form, e.g. packaging.

Preferably, the first and the second pharmaceutical dosage form are adapted for simultaneous or sequential administration, wherein the first pharmaceutical dosage form may be administered before or after the second pharmaceutical dosage form and wherein the first and the second pharmaceutical dosage form are administered either *via* the same or a different pathway of administration.

For the purpose of specification, the term "simultaneous administration" preferably refers to an administration of the first and the second pharmaceutical dosage form within a time span of 15 minutes from each other, whereas the term "sequential administration" preferably refers to an administration of the first and the second pharmaceutical dosage form within a time span of more than 15 minutes from each other.

In a preferred embodiment, the first and the second pharmaceutical dosage form are adapted for administration to the patient *via* the same pathway.

In another preferred embodiment, the first and the second pharmaceutical dosage form are adapted for administration to the patient *via* different pathways.

In a preferred embodiment, the first and the second pharmaceutical dosage form are administered simultaneously.

In another preferred embodiment, the first and the second pharmaceutical dosage form are administered sequentially.

In a preferred embodiment, the first and/or the second pharmaceutical dosage form are adapted for once daily administration.

In another preferred embodiment, the first and/or the second pharmaceutical dosage form are adapted for multiple daily administration, in particular twice daily or thrice daily.

In a preferred embodiment, the first pharmaceutical dosage form is adapted for once daily administration and the second pharmaceutical dosage form is adapted for multiple daily, in particular twice daily or thrice daily, administration.

Suitable pathways of administration of the pharmaceutical dosage forms contained in the kit include but are not limited to oral, intravenous, intraperitoneal, intradermal, intrathecal, intramuscular, intranasal, transmucosal, subcutaneous, and/or rectal administration.

In a preferred embodiment, one or both of the pharmaceutical dosage forms contained in the kit are for oral administration.

In another preferred embodiment, one or both of the pharmaceutical dosage forms contained in the kit are for parenteral administration, in particular intravenous, intraperitoneal, intrathecal, intramuscular, or subcutaneous administration.

In a preferred embodiment, the first and the second pharmaceutical dosage form are for oral, simultaneous administration once daily.

In another preferred embodiment, the first and the second pharmaceutical dosage form are for oral, simultaneous administration multiple daily, in particular twice daily or thrice daily.

In still another preferred embodiment, the first and the second pharmaceutical dosage form are each for oral, sequential administration once daily.

In a preferred embodiment, the first and the second pharmaceutical dosage form are for sequential administration once daily each, where the first and the second pharmaceutical dosage form are adapted for administration *via* different pathways, e.g. oral and parenteral administration.

In another preferred embodiment, the first and the second pharmaceutical dosage form are each for oral, sequential administration multiple daily, in particular twice daily or thrice daily.

In another preferred embodiment, the first and the second pharmaceutical dosage form are for sequential administration multiple daily each, in particular twice daily or thrice daily, where the first and the second pharmaceutical dosage form are adapted for administration *via* different pathways, e.g. oral and parenteral administration.

The following examples further illustrate the invention but are not to be construed as limiting its scope.

Pharmacological methods:

In the following, the first pharmacologically active ingredient (1r,4r)-6'-fluoro-N,N-dimethyl-4-phenyl-4',9'-dihydro-3'H-spiro[cyclohexane-1,1'-pyrano[3,4,b]indol]-4-amine was employed in form of the hemicitrate salt. Therefore, all amounts of the first pharmacologically active ingredient are specified with respect to the hemicitrate salt.

As the second pharmacologically active ingredient, Indometacin or Diclofenac sodium were employed. All amounts are specified accordingly.

Example 1: Paw incision model in rats (postoperative pain)

The experiments were carried out in male albino rats (Sprague Dawley) with 170 g - 230 g body weight from a commercial breeder (Janvier; France). The animals were housed under standardized conditions: light/dark rhythm (06.00 h - 18.00 h light, 18.00 h - 06.00 h dark); room temperature 20°C - 24°C; relative air humidity 35% - 70%; 15 air changes per hour, air movement <0.2 m/sec. The animals were given tap water and a diet of standard laboratory food (Ssniff R/M-Haltung, Ssniff Spezialdiäten GmbH, Soest, Germany) *ad libitum*. Both were withdrawn during the test. All rats were used only once. Ten rats were used per experimental group. There were at least five days between delivery of the animals and the day of surgery.

The rats were placed in a plastic cage with a wire mesh bottom which allowed full access to the paws. Hind paw withdrawal threshold after mechanical stimulation was tested with electronic von Frey hairs (Somedic Sales AB, Hörby, Sweden). Animals were placed in a plastic cage with a wire mesh bottom which allowed full access to the paws. Behavioral accommodation was allowed for 30 min. In each case, withdrawal response was measured at an area adjacent to the wound (ipsilateral) and to the same area on the non-injured foot (contralateral). Two hours after surgery, primary hypersensitivity was tested as tactile withdrawal threshold shortly before drug administration and at different time points after drug application. Animals injected with vehicle served as controls. The pretest measurement was made prior to surgery and two thresholds were taken per test and averaged.

Surgery was performed as previously described (Brennan T.J., Vandermeulen E.P., and Gebhart G.F., Characterization of a rat model of incisional pain, Pain 1996; 64:493-501).

Briefly, rats were anaesthetised with isoflurane, and a 1 cm longitudinal incision was made, through skin and fascia of the plantar aspect of the foot, starting from the proximal edge of the heel and extending toward the metatarsal toes. The plantaris muscle was elevated and incised longitudinally. The muscle origin and insertion remained intact. After spreading of the muscle and haemostasis with gentle pressure, the skin was closed with two single interrupted sutures. After surgery, the rats were allowed to recover in their home cages and the animals regained consciousness within 2 to 5 minutes. In order to ensure a complete recovery from anaesthesia the baseline value of each individual animal was recorded not until 2 hours after surgery.

The first pharmacologically active ingredient was dissolved in 5% DMSO and 95% glucose solution (5%). The second pharmacologically active ingredient was dissolved in 1% CMC in aqua dest. Intravenous (i.v.) and intraperitoneal (i.p.) applications were made in a volume of 5 mL/kg.

Data were recorded and the median was calculated from five values of each animal and measurement.

The median values of the individual latencies are calculated as the percentage of the Maximum Possible Effect (%MPE) according to the following formula:

$$\%MPE = 100 - [(value\ after\ application - pretest\ before\ surgery) / (pretest\ after\ surgery - pretest\ before\ surgery) \cdot 100]$$

The individual %MPE values were averaged for the respective treatment group and expressed as mean %MPE $\pm$ standard error of the mean (SEM).

The pharmacologically active ingredients were administered using a logarithmically staggered dose scheme. The results are presented in graphs as means $\pm$ SEM against the time after surgery.

Data were analyzed by means of two-factor analysis of variance (ANOVA) with repeated measures. Significance of treatment-, time- or treatment x time interaction effects was analyzed by means of Wilks' Lambda statistics. In case of a significant treatment effect, pair-wise comparison was performed at the different time points effect by Fisher's least significant difference test. Results were considered statistically significant if $p < 0.05$.

ED₂₅- and ED₅₀-values were determined by regression analysis in case of dose-dependent results (according to Litchfield J.T. and Wilcoxon F.A., A simplified method of evaluating dose-effect experiments, J. Pharmacol. Exp. Ther. 1949; 96: 99-113). The analysis of the results with respect to a supra-additive effect of the first and the second pharmacologically active ingredient according to the invention is carried out *via* statistical comparison of the theoretical additive ED₂₅- and ED₅₀-value or by comparison of the theoretically additive effect of defined doses of the first and the second pharmacologically active ingredient with the experimental determined effect of their combination. If an ED₂₅- and ED₅₀-value could be calculated, a statistical comparison of the theoretical ED₂₅- and ED₅₀-value with the experimentally determined ED₂₅- and ED₅₀-value of a so-called fixed ratio combination was

carried out (isobolographic analysis according to Tallarida J.T., Porreca F., and Cowan A., Statistical analysis of drug-drug and site-site interactions with isobolograms, Life Sci. 1989; 45: 947-961).

The interaction studies presented herein were performed by comparison of the theoretically additive effect of defined doses of the first and the second pharmacologically active ingredient with the experimental determined effect of their combination.

The application route was intravenous (i.v.) for the first pharmacologically active ingredient and intraperitoneal (i.p.) for the second pharmacologically active ingredient.

Tests were performed using doses of 0.0021 mg/kg body weight to 0.01 mg/kg body weight of the first pharmacologically active ingredient and 46.4 mg/kg body weight of Indometacin or 147 mg/kg of Diclofenac sodium as the second pharmacologically active ingredient.

The time point of efficacy-calculation in case of the combined administration of the first and the second pharmacologically active ingredient according to the invention corresponds to the timepoint of the peak effect of the respective pharmacologically active ingredient. The effect of the experiments with fixed dose combinations showed higher experimental determined efficacy than the theoretically calculated efficacy. Thus, the combination studies demonstrate significant synergistic interaction of the first pharmacologically active ingredient with the second pharmacologically active ingredient.

a) Indometacin as second pharmacologically active ingredient

When administered in combination, the first pharmacologically active ingredient (0.0021 to 0.01 mg/kg body weight i.v.) and Indomethacin as the second pharmacologically active ingredient (46.4 mg/kg body weight i.p.) showed a dose dependent analgesic efficacy with a maximal effect of 68 % MPE at 30 min.

The analysis showed significant synergistic interaction of the first pharmacologically active ingredient and Indometacin as the second pharmacologically active ingredient with an ED₂₅-value of 46.404 mg/kg (46.403-46.405) i.v./i.p. and an ED₅₀-value of 46.408 mg/kg (46.407-46.408) i.v./i.p.

Figure 1 shows the withdrawal threshold in g in dependence of the time elapsed after administration.

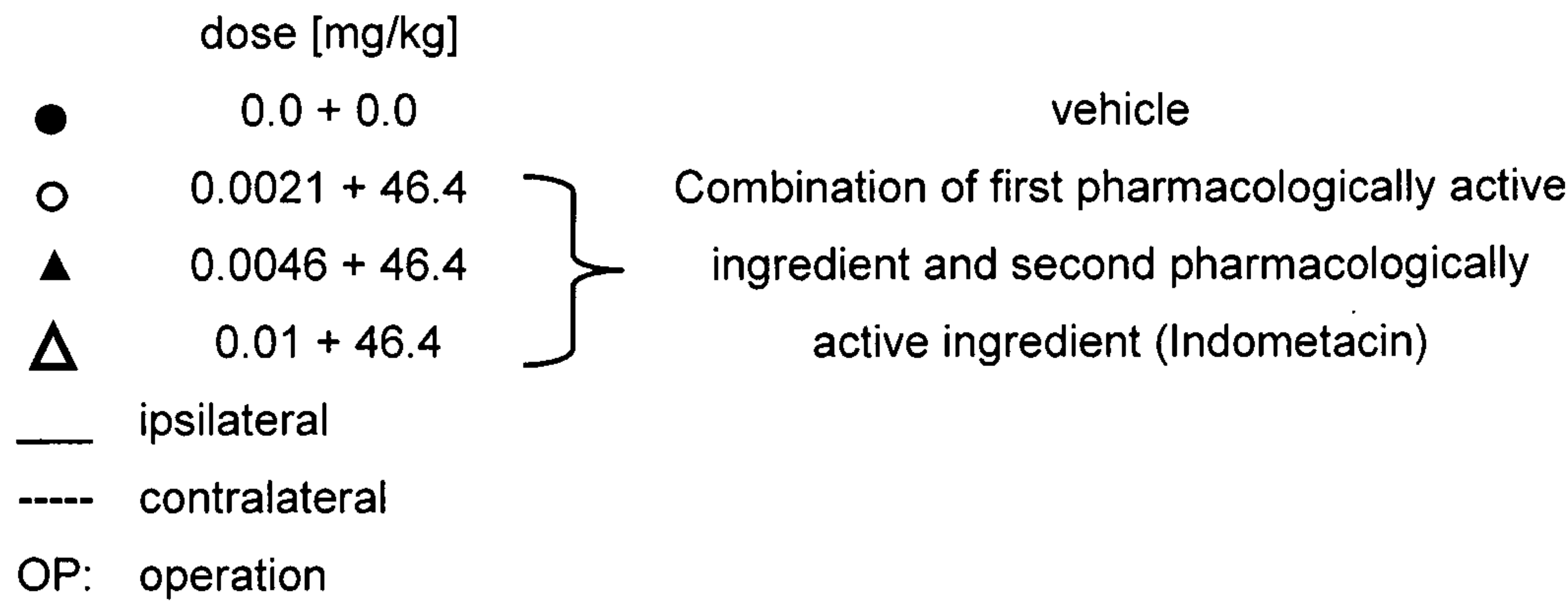


Figure 2 shows % MPE (Maximum possible effect) of the first and the second pharmacologically active ingredient and of the combined administration of the first and the second pharmacologically active ingredient, and the theoretical % MPE of the combined administration of the first and the second pharmacologically active ingredient in dependence of the time post administration.

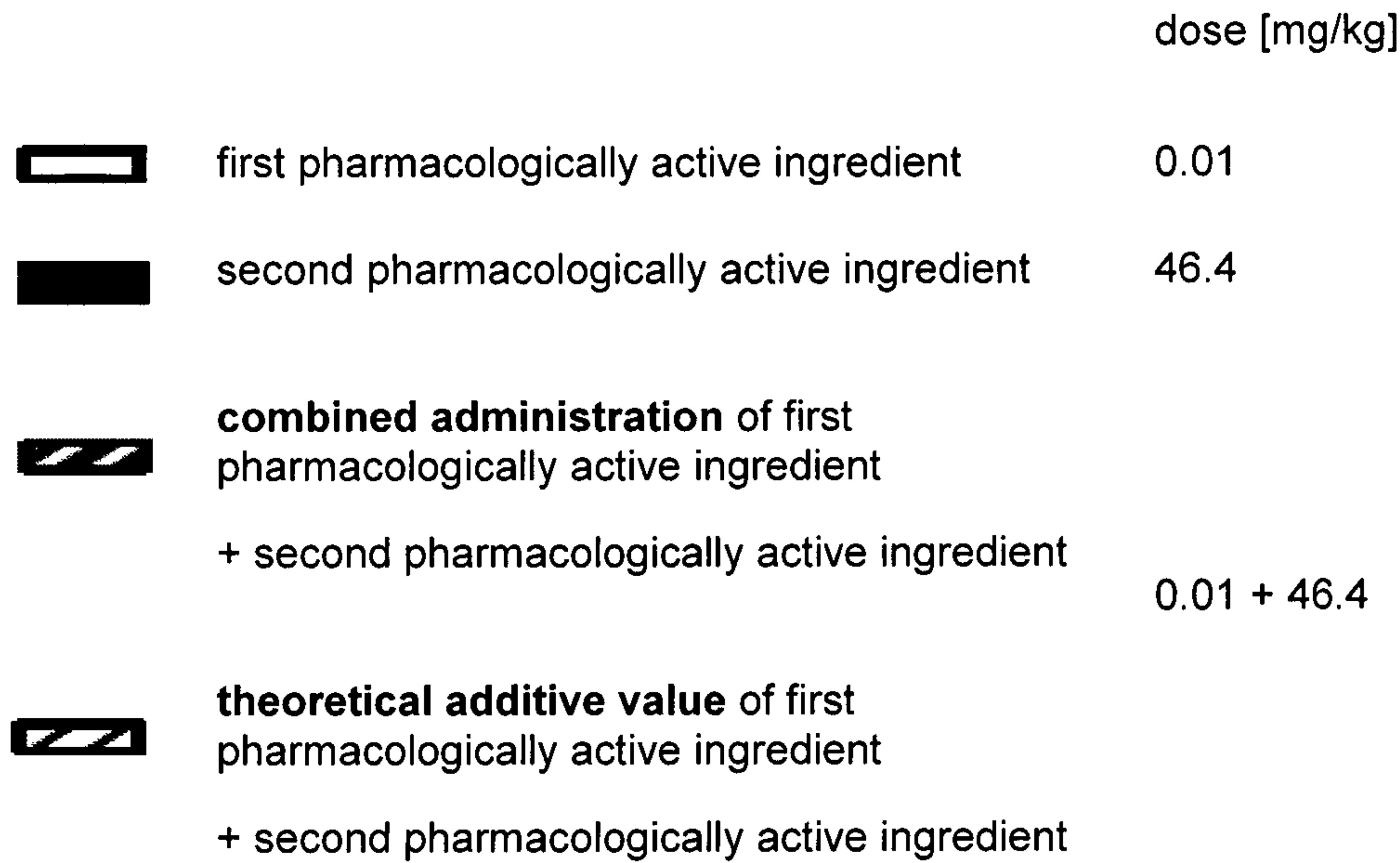


Figure 3 shows % MPE (Maximum possible effect) of the first and the second pharmacologically active ingredient and of the combined administration of the first and the second pharmacologically active ingredient, and the theoretical % MPE of the combined administration of the first and the second pharmacologically active ingredient in dependence of the time post administration.

dose [mg/kg]

	first pharmacologically active ingredient	0.0046
	second pharmacologically active ingredient	46.4
	combined administration of first pharmacologically active ingredient + second pharmacologically active ingredient	0.0046 + 46.4
	theoretical additive value of first pharmacologically active ingredient + second pharmacologically active ingredient	

Experimental results demonstrating supra-additive effect of the combination of the first and the second pharmacologically active ingredient are summarized in the following tables 1 to 5.

Table 1: data corresponding to figure 1

% MPE (Maximum possible effect) of the combined administration of different doses of the first and the second pharmacologically active ingredient in dependence of the time post administration:

%MPE				
	dose [mg/kg]	30 min. (n = 10)	60 min. (n = 10)	90 min. (n = 10)
		Mean SEM	Mean SEM	Mean SEM
vehicle	0.0 + 0.0	-0.41 ± 0.70	-0.09 ± 0.65	-0.08 ± 0.80
Combination of first pharmacologically active ingredient and second pharmacologically active ingredient (Indometacin)	0.0021 + 46.4	11.1 ± 3.68 p ≤ 0.01	2.81 ± 1.33 n.s.	0.48 ± 0.65 n.s.
	0.00464 + 46.4	27.7 ± 4.54 p ≤ 0.001	41.8 ± 4.86 p ≤ 0.001	23.7 ± 3.84 p ≤ 0.001
	0.01 + 46.4	67.5 ± 2.78 p ≤ 0.001	61.8 ± 3.78 p ≤ 0.001	37.1 ± 4.42 p ≤ 0.001

p: level of statistical significance; n.s. : not significant

Table 2: data corresponding to figure 1

% MPE : GLM Repeated Measures and Statistical evaluation of the data following two-factor analysis of variance (ANOVA) and Fisher's LSD:

GLM (General Linear Model) %MPE			
treatment		time	interaction
F(3,36) = 107.815		F(2,72) = 30.510	F(6,72) = 12.989
p < 0.001		p < 0.001	p < 0.001
ANOVA [Fisher's LSD]			
dose [mg/kg]	30 min.	60 min.	90 min.
0.0021 + 46.4	p = 0.018	p = 0.521	p = 0.896
0.00464 + 46.4	p < 0.001	p < 0.001	p < 0.001
0.01 + 46.4	p < 0.001	p < 0.001	p < 0.001

p: level of statistical significance.

Table 3: data corresponding to figure 1

ipsilateral : GLM Repeated Measures and Statistical evaluation of the data following two-factor analysis of variance (ANOVA) and Fisher's LSD:

GLM (General Linear Model) ipsilateral			
treatment	time		interaction
F(3,36) = 112.415 p < 0.001	F(2,72) = 30.329 p < 0.001		F(6,72) = 12.898 p < 0.001
ANOVA [Fisher's LSD]			
dose [mg/kg]	30 min.	60 min.	90 min.
0.0021 + 46.4	p = 0.017	p = 0.500	p = 0.886
0.00464 + 46.4	p < 0.001	p < 0.001	p < 0.001
0.01 + 46.4	p < 0.001	p < 0.001	p < 0.001

p: level of statistical significance.

Table 4: data corresponding to figure 1

contralateral : GLM Repeated Measures and Statistical evaluation of the data following two-factor analysis of variance (ANOVA) and Fisher's LSD:

GLM (General Linear Model) contralateral			
treatment		time	interaction
F(3,36) = 23.975 p < 0.001		F(2,72) = 18.175 p < 0.001	F(6,72) = 12.331 p < 0.001
ANOVA [Fisher's LSD]			
dose [mg/kg]	30 min.	60 min.	90 min.
0.0021 + 46.4	p = 0.442	p = 0.517	p = 0.388
0.00464 + 46.4	p = 0.020	p = 0.027	p = 0.004
0.01 + 46.4	p < 0.001	p < 0.001	p = 0.019

p: level of statistical significance.

Table 5:

% MPE (Maximum possible effect) of the first and the second pharmacologically active ingredient and of the combined administration of the first and the second pharmacologically active ingredient, and the theoretical % MPE of the combined administration of different doses of the first and the second pharmacologically active ingredient in dependence of the time post administration and analysis of the interaction between the first and the second pharmacologically active ingredient:

%MPE				
	dose [mg/kg]	30 min. (n = 10)	60 min. (n = 10)	90 min. (n = 10)
		Mean SEM	Mean SEM	Mean SEM

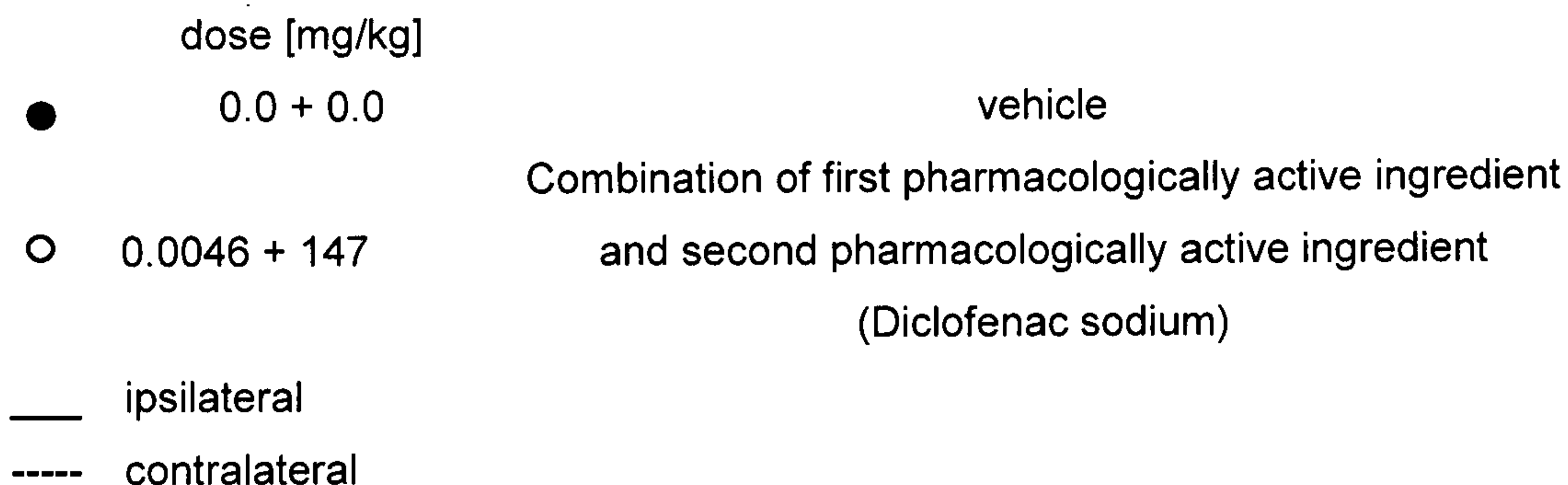
first pharmacologically active ingredient	0.01	43.2 ± 2.61	34.1 ± 4.88	7.71 ± 2.23
	0.0046	12.2 ± 2.69	10.6 ± 3.51	2.88 ± 2.27
second pharmacologically active ingredient (Indometacin)	46.4	8.12 ± 1.31	14.1 ± 1.98	3.7 ± 1.16
combination of first pharmacologically active ingredient and second pharmacologically active ingredient (Indometacin)	0.01/46.4	67.5 ± 2.78 (theoretical additive value: 51.3 ± 2.92)	61.8 ± 3.78 (theoretical additive value: 48.2 ± 5.26)	37.1 ± 4.42 (theoretical additive value: 11.4 ± 2.51)
	0.0046/46.4	27.7 ± 4.54 (theoretical additive value: 20.3 ± 2.99)	41.8 ± 4.86 (theoretical additive value: 24.7 ± 4.03)	23.7 ± 3.84 (theoretical additive value: 6.57 ± 2.55)

b) *Diclofenac sodium as second pharmacologically active ingredient*

When administered in combination, the first pharmacologically active ingredient (0.0046 mg/kg body weight i.v.) and Diclofenac sodium as the second pharmacologically active ingredient (147 mg/kg body weight i.p.) showed an analgesic efficacy with a maximal effect of 26 % MPE at 90 min.

The analysis showed synergistic interaction of the first pharmacologically active ingredient and Diclofenac sodium as the second pharmacologically active ingredient 90 min post administration.

Figure 4 shows the withdrawal threshold in g in dependence of the time elapsed after administration.



OP: operation

Figure 5 shows % MPE (Maximum possible effect) of the first and the second pharmacologically active ingredient and of the combined administration of the first and the second pharmacologically active ingredient, and the theoretical % MPE of the combined administration of the first and the second pharmacologically active ingredient in dependence of the time post administration.

	dose [mg/kg]
 first pharmacologically active ingredient	0.0046
 second pharmacologically active ingredient	147
 combined administration of first pharmacologically active ingredient + second pharmacologically active ingredient	0.0046 + 147
 theoretical additive value of first pharmacologically active ingredient + second pharmacologically active ingredient	

Experimental results demonstrating supra-additive effect of the combination of the first and the second pharmacologically active ingredient are summarized in the following tables 6 to 10.

Table 6: data corresponding to figure 4

% MPE (Maximum possible effect) of the combined administration of the first and the second pharmacologically active ingredient in dependence of the time post administration:

%MPE				
	dose [mg/kg]	30 min. (n = 10)	60 min. (n = 10)	90 min. (n = 10)
		Mean SEM	Mean SEM	Mean SEM
vehicle	0.0 + 0.0	-0.31 ± 0.54	-0.26 ± 0.60	-0.36 ± 0.69

combination of first pharmacologically active ingredient and second pharmacologically active ingredient (Diclofenac sodium)	0.0046 + 147	18.7 ± 3.26 p ≤ 0.001	21.6 ± 4.63 p ≤ 0.001	26.4 ± 8.49 p ≤ 0.01
---	--------------	--------------------------	--------------------------	-------------------------

p: level of statistical significance

Table 7: data corresponding to figure 4

% MPE : GLM Repeated Measures and Statistical evaluation of the data following two-factor analysis of variance (ANOVA) and Fisher's LSD:

GLM (General Linear Model) %MPE			
treatment	time		interaction
F(1,18) = 23.086 p < 0.001	F(2,36) = 0.759 p = 0.476		F(6,36) = 0.783 p = 0.465
ANOVA [Fisher's LSD]			
dose [mg/kg]	30 min.	60 min.	90 min.
0.0046 + 147	p = 0.001	p = 0.001	p = 0.006

p: level of statistical significance.

Table 8: data corresponding to figure 4

ipsilateral : GLM Repeated Measures and Statistical evaluation of the data following two-factor analysis of variance (ANOVA) and Fisher's LSD:

GLM (General Linear Model) ipsilateral			
treatment	time		interaction
F(1,18) = 26.072 p < 0.001	F(2,36) = 0.725 p = 0.491		F(2,36) = 0.740 p = 0.484
ANOVA [Fisher's LSD]			
dose	30 min.	60 min.	90 min.

[mg/kg]			
0.0046 + 147	p < 0.001	p < 0.001	p = 0.005

p: level of statistical significance.

Table 9: data corresponding to figure 4

contralateral : GLM Repeated Measures and Statistical evaluation of the data following two-factor analysis of variance (ANOVA) and Fisher's LSD:

GLM (General Linear Model) contralateral			
treatment	time		interaction
F(1,18) = 9.522 p = 0.006	F(2,36) = 2.094 p = 0.138		F(2,36) = 1.594 p = 0.217
ANOVA [Fisher's LSD]			
dose [mg/kg]	30 min.	60 min.	90 min.
0.0046 + 147	p = 0.158	p = 0.004	p = 0.023

p: level of statistical significance.

Table 10:

% MPE (Maximum possible effect) of the first and the second pharmacologically active ingredient and of the combined administration of the first and the second pharmacologically active ingredient, and the theoretical % MPE of the combined administration of the first and the second pharmacologically active ingredient in dependence of the time post administration and analysis of the interaction between the first and the second pharmacologically active ingredient:

%MPE				
	dose [mg/kg]	30 min. (n = 10)	60 min. (n = 10)	90 min. (n = 10)
		Mean SEM	Mean SEM	Mean SEM

first pharmacologically active ingredient	0.0046	12.2 ± 2.69	10.6 ± 3.51	2.88 ± 2.27
second pharmacologically active ingredient (Diclofenac sodium)	147	11.4 ± 2.1	0.69 ± 0.87	-0.66 ± 0.77
Combination of first pharmacologically active ingredient and second pharmacologically active ingredient (Diclofenac sodium)	0.0046/147	18.7 ± 3.26 (theoretical additive value: 23.6 ± 3.41)	21.6 ± 4.63 (theoretical additive value: 11.3 ± 3.61)	26.4 ± 8.49 (theoretical additive value: 2.22 ± 2.39)

Example 2: Randall Selitto test in rats

The weight ratios of the first and the second pharmacologically active ingredient that will lead to a supra-additive effect (synergistic effect) may be determined *via* the test of Randall and Selitto as described in Arch. Int. Pharmacodyn., 1957, 111: 409-419, which is a model for inflammatory pain. The respective part of the literature is hereby incorporated by reference and forms part of the present disclosure.

By means of injection of 0.1 ml of Carrageenin-suspension ventrally into a hind paw of a rat an oedema is induced, on which pain is generated 4 hours later by continuously increasing pressure with a stamp (2 mm tip diameter). The antinociceptive and antihyperalgesic activity of the tested pharmacologically active ingredient is determined at different points in time after administration of the pharmacologically active ingredient. The measured value to be determined and at the same time also the end point of the pain test is the pressure at which the vocalisation reaction of the rat occurs. The percentage maximum possible effect (%MPE) is calculated. The maximum pressure of the stamp is 250 g. The group size is $n = 12$.

ED₅₀ values were determined by regression analysis in case of dose-dependent results (according to Litchfield J.T. and Wilcoxon F.A., A simplified method of evaluating dose-effect experiments, J. Pharmacol. Exp. Ther. 1949; 96: 99-113). The analysis of the results with respect to a supra-additive effect of the first and the second pharmacologically active ingredient according to the invention is carried out *via* statistical comparison of the theoretical additive ED₅₀-value with the experimentally determined ED₅₀-value of a so-called fixed ratio combination (isobolographic analysis according to Tallarida J.T., Porreca F., and Cowan A.,

Statistical analysis of drug-drug and site-site interactions with isobolograms, Life Sci. 1989; 45: 947-961).

The interactions studies presented herein were performed using equieffective doses of the first and the second pharmacologically active ingredient, calculated from the ratio of the respective ED₅₀ values of the first and the second pharmacologically active ingredient if administered alone.

The application route was intravenous (i.v.) for the first pharmacologically active ingredient and intraperitoneal (i.p.) for the second pharmacologically active ingredient. The first and the second pharmacologically active ingredient were dissolved in 5% DMSO, 5% Cremophor, 90% glucose solution (5%) and in 1% CMC in aqua dest., respectively. Intravenous (i.v.) and intraperitoneal (i.p.) applications were made in a volume of 5 mL/kg.

In case of the combined, simultaneous administration, the relative dose ratio of first pharmacologically active ingredient to the second pharmacologically active ingredient was 1 : 47,764 (Indometacin) and 1 : 38,379 (Diclofenac sodium), respectively.

Thus, the time point of ED₅₀ calculation in case of the combined administration of the first and the second pharmacologically active ingredient according to the invention corresponds to the timepoint of the peak effect of the respective pharmacologically active ingredient. The isobolographic analysis revealed that the experimental ED₅₀-values regarding the combined administration of the first and the second pharmacologically active ingredient were significantly lower than the respective theoretical ED₅₀-values. Thus, the combination studies demonstrate significant synergistic interaction of the first pharmacologically active ingredient with the second pharmacologically active ingredient.

a) Indometacin as second pharmacologically active ingredient

When the first pharmacologically active ingredient (1*r*,4*r*)-6'-fluoro-N,N-dimethyl-4-phenyl-4',9'-dihydro-3'H-spiro[cyclohexane-1,1'-pyrano-[3,4,*b*]indol]-4-amine in form of the hemicitrate salt was applied alone, the peak effect was reached 15 min p. appl. (timepoint of first measurement) and ED₅₀-value of 3.38 (3.01 – 3.74) µg/kg i.v. was calculated. The second pharmacologically active ingredient Indometacin induced a dose-dependent analgesic effect with ED₅₀-values of 161,327 (149,231 – 174,347) µg/kg i.p., reaching the peak effect 120 min p. appl. According to their respective timepoint of peak effect, the first pharmacologically active ingredient was applied 15 min and the second pharmacologically

active ingredient 120 min before timepoint of measurement of the interaction-experiments (i. e. the second pharmacologically active ingredient was applied 105 min before the first pharmacologically active ingredient).

Thus, the time point of ED₅₀ calculation of the pharmaceutical composition according to the invention corresponds to the timepoint of the peak effect of the respective pharmacologically active ingredient. The isobolographic analysis revealed that in case of the combined administration of the first and the second pharmacologically active ingredient the experimental ED₅₀-values were significantly lower than the respective theoretical ED₅₀-values. Thus, the combination studies demonstrate significant synergistic interaction of the first pharmacologically active ingredient with Indometacin as the second pharmacologically active ingredient. The results of the isobolographic analysis are summarized in the following table 11.

Figure 6 shows the graphical analysis of experimental ED₅₀-values corresponding to the single administration of the first pharmacologically active ingredient and of Indometacin as the second pharmacologically active ingredient, respectively, and the corresponding theoretic additive values for the combined administration of the first and the second pharmacologically active ingredient compared to the experimental ED₅₀-values determined for said combination.

		ED ₅₀ (95% CI)[μg/kg] (i.v./i.p.)
first pharmacologically active ingredient	=	3.38 (3.01 – 3.74)
second pharmacologically active ingredient	=	161,327 (149,231 – 174,347)
■ theoretical additive value	=	80,670 (75,383 – 85,957)
part of first pharmacologically active ingredient	=	1.69 (1.58 – 1.80)
part of second pharmacologically active ingredient	=	80,669 (75,382 – 85,956)
● experimental value of the combination	=	44,323 (41,854 – 46,639)
part of first pharmacologically active ingredient	=	0.928 (0.828 – 1.03)
part of second pharmacologically active ingredient	=	44,322 (40,869 – 47,774)

Table 11:

Experimental ED₅₀ values of the first and the second pharmacologically active ingredient and isobolographic analysis of the interaction between the first and the second pharmacologically active ingredient:

Substance / ED ₅₀ [µg/kg] (confidence interval)				
first pharmacologically active ingredient	second pharmacologically active ingredient	Theoretical ED ₅₀ [µg/kg] of the combination	Experimental ED ₅₀ [µg/kg] of the combination	Interaction
3.38 (3.01 – 3.74)	161,327 (149,231 – 174,347)	80,670 (75,383 – 85,957)	44,323 (41,854 – 46,639)	supra- additive (p<0.001)

p: level of statistical significance.

b) *Diclofenac sodium as second pharmacologically active ingredient*

When the first pharmacologically active ingredient was applied alone, the peak effect was reached 15 min p. appl. (timepoint of first measurement) and ED₅₀-value of 3.31 (2.85 – 3.75) µg/kg i.v. was calculated. The second pharmacologically active ingredient Diclofenac sodium induced a dose-dependent analgesic effect with ED₅₀-values of 127,036 (119,433 – 137,447) µg/kg i.p., reaching the peak effect 120 min p. appl. According to their respective timepoint of peak effect, the first pharmacologically active ingredient was applied 15 min and the second pharmacologically active ingredient 120 min before timepoint of measurement of the interaction-experiments (i. e. the second pharmacologically active ingredient was applied 105 min before the first pharmacologically active ingredient). Thus, the time point of ED₅₀ calculation of the pharmaceutical composition according to the invention corresponds to the timepoint of the peak effect of the respective pharmacologically active ingredient. The isobolographic analysis revealed that in case of the combined administration of the first and the second pharmacologically active ingredient the experimental ED₅₀-values were significantly lower than the respective theoretical ED₅₀-values. Thus, the combination studies demonstrate significant synergistic interaction of the first pharmacologically active ingredient with Diclofenac sodium as the second pharmacologically active ingredient. The results of the isobolographic analysis are summarized in the following table 12.

Figure 7 shows the graphical analysis of experimental ED₅₀-values corresponding to the single administration of the first pharmacologically active ingredient and Diclofenac sodium as the second pharmacologically active ingredient, respectively, and the corresponding theoretic additive values for the combined administration of the first and the second pharmacologically active ingredient compared to the experimental ED₅₀-values determined for said combination.

		ED₅₀ (95% CI)[μg/kg] (i.v./i.p.)
first pharmacologically active ingredient	=	3.31 (2.85 – 3.75)
second pharmacologically active ingredient	=	127,036 (119,433 – 137,447)
■ theoretical additive value	=	63,520 (58,680 – 68,359)
part of first pharmacologically active ingredient	=	1.66 (1.53 – 1.78)
part of second pharmacologically active ingredient	=	63,518 (58,679 – 68,357)
● experimental value of the combination	=	38,780 (32,917 – 38,781)
part of first pharmacologically active ingredient	=	1.01 (0.872 – 1.15)
part of second pharmacologically active ingredient	=	38,780 (35,997 – 41,563)

Table 12:

Experimental ED₅₀ values of the first and the second pharmacologically active ingredient and isobolographic analysis of the interaction between the first and the second pharmacologically active ingredient:

Substance / ED₅₀ [μg/kg] (confidence interval)				
first pharmacologically active ingredient	second pharmacologically active ingredient	Theoretical ED ₅₀ [μg/kg] of the combination	Experimental ED ₅₀ [μg/kg] of the combination	Interaction
3.31 (2.85 – 3.75)	127,036 (119,433 – 137,447)	63,520 (58,680 – 68,359)	38,780 (32,917 – 38,781)	supra- additive (p<0.001)

p: level of statistical significance.

Patent claims:

1. A pharmaceutical composition comprising:
 - (a) a first pharmacologically active ingredient selected from (1r,4r)-6'-fluoro-N,N-dimethyl-4-phenyl-4',9'-dihydro-3'H-spiro[cyclohexane-1,1'-pyrano[3,4,b]indol]-4-amine and the physiologically acceptable salts thereof, and
 - (b) a second pharmacologically active ingredient which is a non-steroidal anti-rheumatic drug selected from the group consisting of indometacin, diclofenac, sulindac, tolmetin, zomepirac, aclofenac, bumadizone, etodolac, lonazolac, fentiazac, acemetacin, difenpiramide, oxametacin, proglumetacin, ketorolac, aceclofenac, bufexamac, mefenamic acid, tolfenamic acid, flufenamic acid, meclofenamic acid, and the physiologically acceptable salts thereof.
2. The pharmaceutical composition according to claim 1, wherein the first pharmacologically active ingredient is (1r,4r)-6'-fluoro-N,N-dimethyl-4-phenyl-4',9'-dihydro-3'H-spiro[cyclohexane-1,1'-pyrano[3,4,b]indol]-4-amine.
3. The pharmaceutical composition according to claim 1 or 2, wherein the second pharmacologically active ingredient is selected from the group consisting of indometacin, diclofenac, and the physiologically acceptable salts thereof.
4. The pharmaceutical composition according to any of the preceding claims, which contains the first and the second pharmacologically active ingredient in such a weight ratio that they will exert a synergistic therapeutic effect upon administration to a patient.
5. The pharmaceutical composition according to any of the preceding claims, wherein the relative weight ratio of the first pharmacologically active ingredient to the second pharmacologically active ingredient is within the range of from 1 : 2 to 1 : 1,000,000.
6. The pharmaceutical composition according to any of the preceding claims for use in the prevention or treatment of pain.
7. The pharmaceutical composition according to claim 6, wherein the pain is:
 - peripheral, central or muscle skeletal pain; and/or
 - acute, subacute or chronic pain; and/or
 - moderate to severe pain; and/or

- neuropathic or psychogenic or nociceptive or mixed pain; and/or
 - low back pain, visceral pain or headache; and/or
 - post-operative (post-surgical), cancer or inflammatory pain.
8. A pharmaceutical dosage form comprising the pharmaceutical composition according to any of the preceding claims.
 9. The pharmaceutical dosage form according to claim 8, which contains the first pharmacologically active ingredient in a dose of from 10 to 1,200 µg.
 10. The pharmaceutical dosage form according to claim 8 or 9, which contains the second pharmacologically active ingredient in a dose of from 10 to 1,000 mg.
 11. The pharmaceutical dosage form according to any of claims 8 to 10, wherein the dosage of the first pharmacologically active ingredient is within the range of from 1:20 to 20:1 of the amount which is equieffective to the dosage of the second pharmacologically active ingredient.
 12. The pharmaceutical dosage form according to any of claims 8 to 11, which is for oral, intravenous, intraperitoneal, transdermal, intrathecal, intramuscular, intranasal, transmucosal, subcutaneous, or rectal administration.
 13. The pharmaceutical dosage form according to any of claims 8 to 12, which provides under *in vitro* conditions immediate release or controlled release of the first pharmacologically active ingredient and/or the second pharmacologically active ingredient.
 14. A kit comprising a first pharmaceutical dosage form comprising the first pharmacologically active ingredient as defined in claim 1 or 2, and a second pharmaceutical dosage form comprising the second pharmacologically active ingredient as defined in claim 1 or 3.
 15. The kit according to claim 14, wherein the first and the second pharmaceutical dosage form are adapted for simultaneous or sequential administration, either by the same or a different pathway of administration.

Figure 1

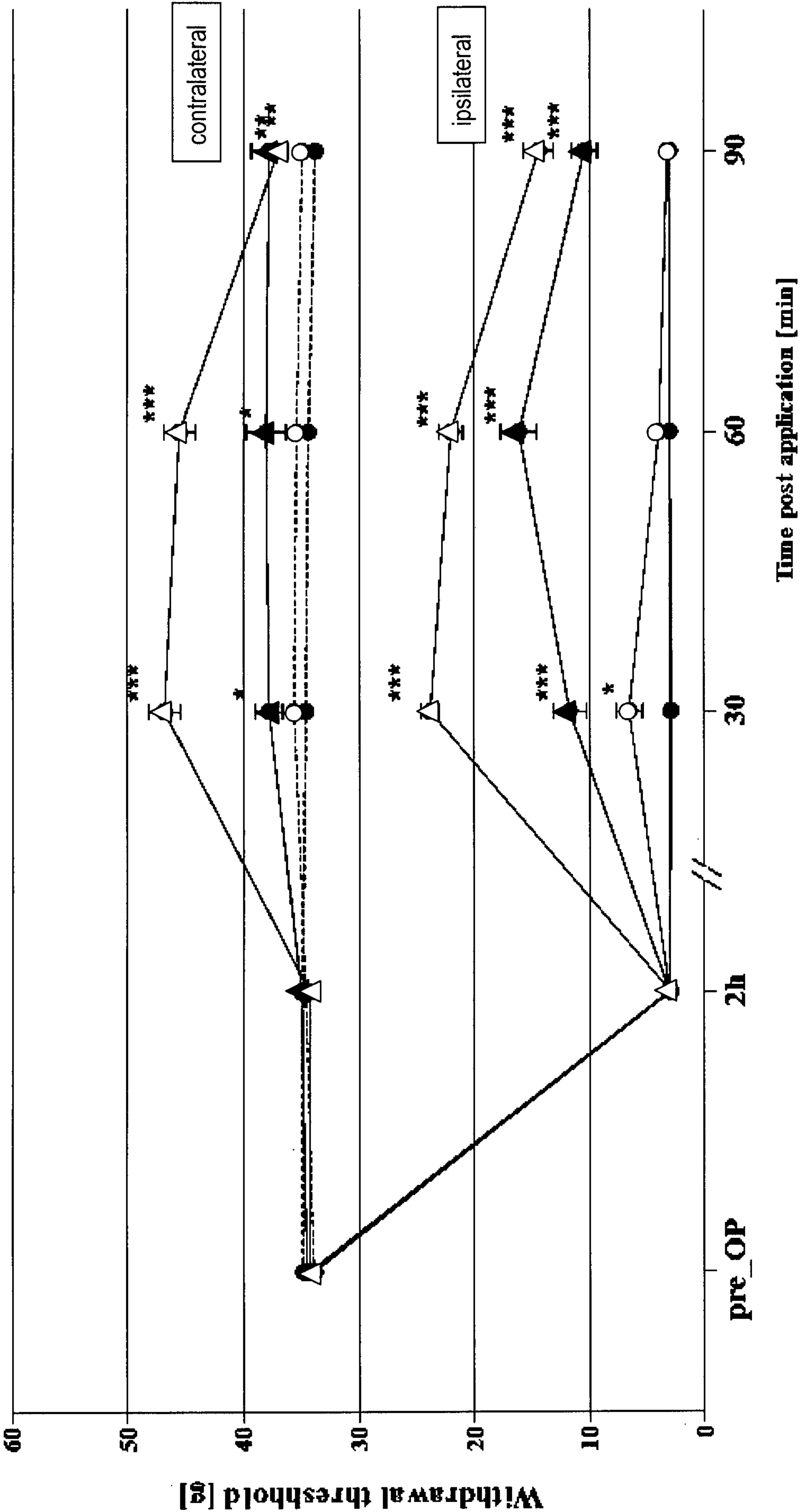


Figure 2

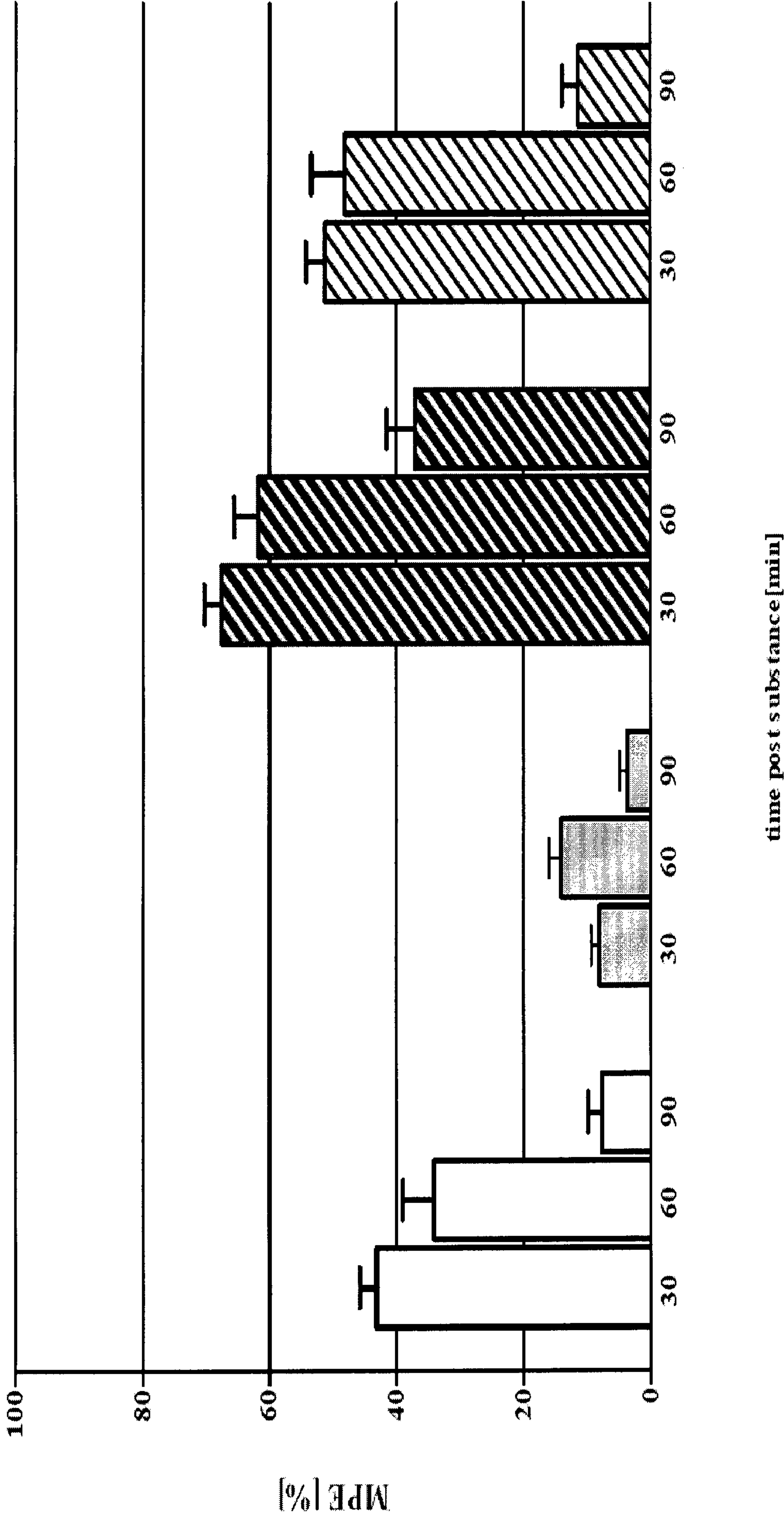


Figure 3

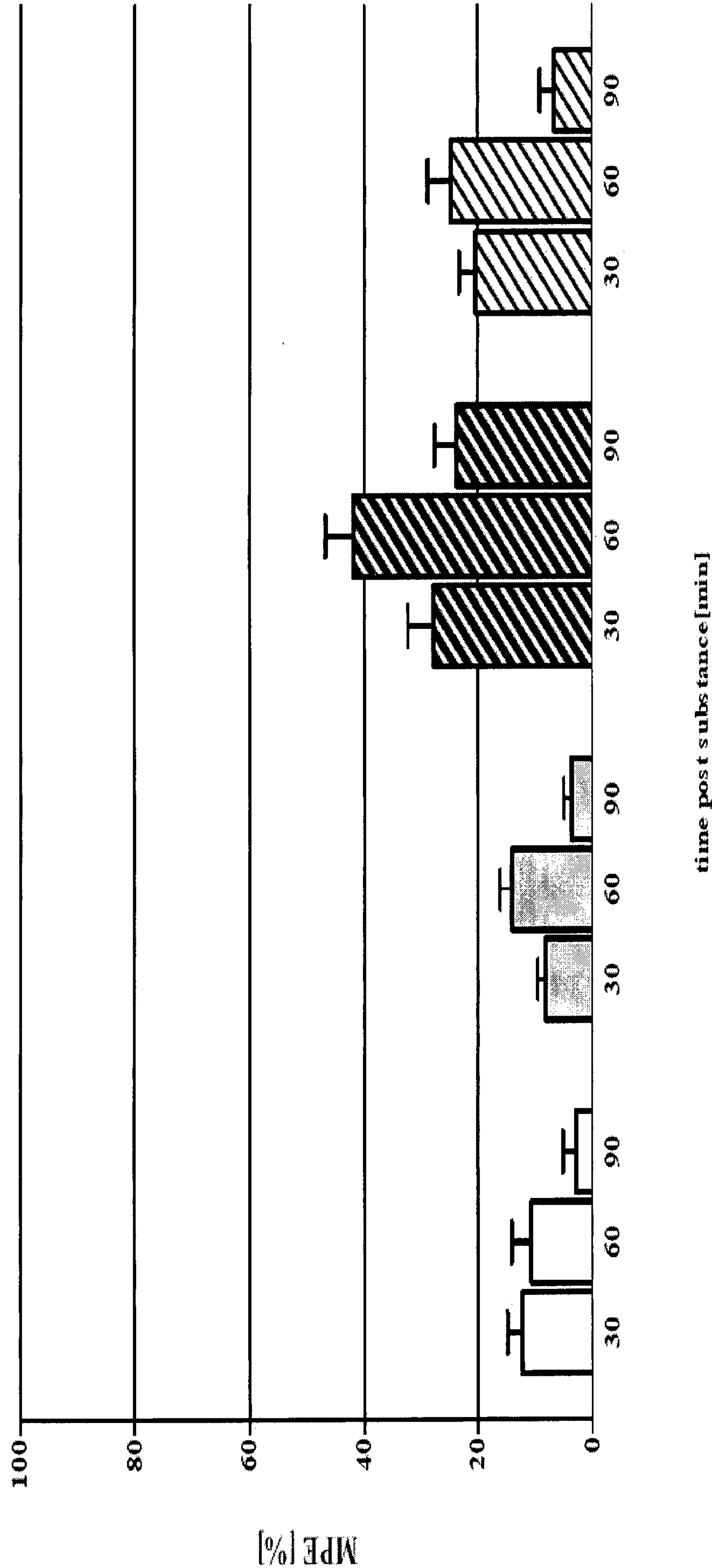


Figure 4

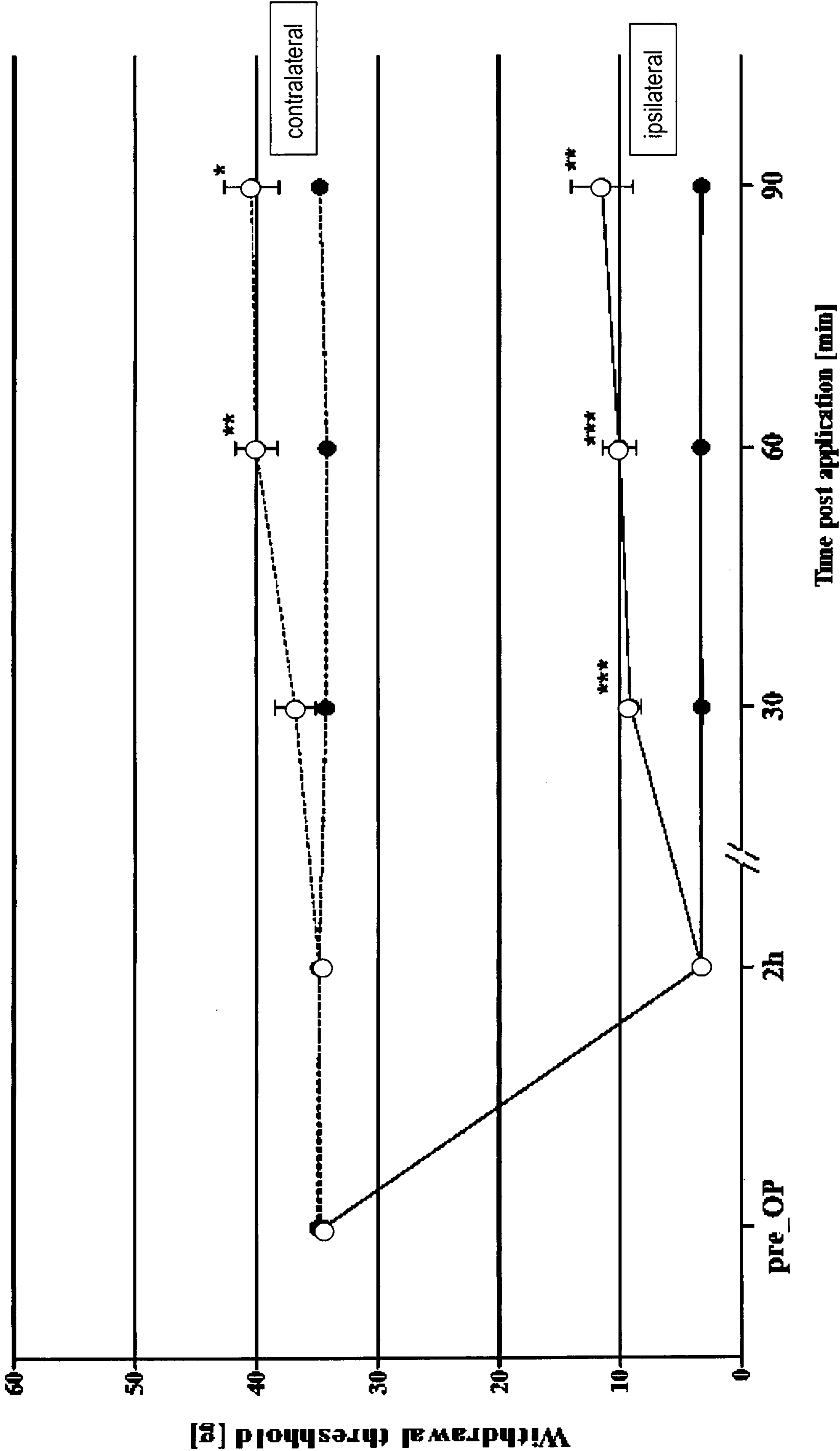


Figure 5

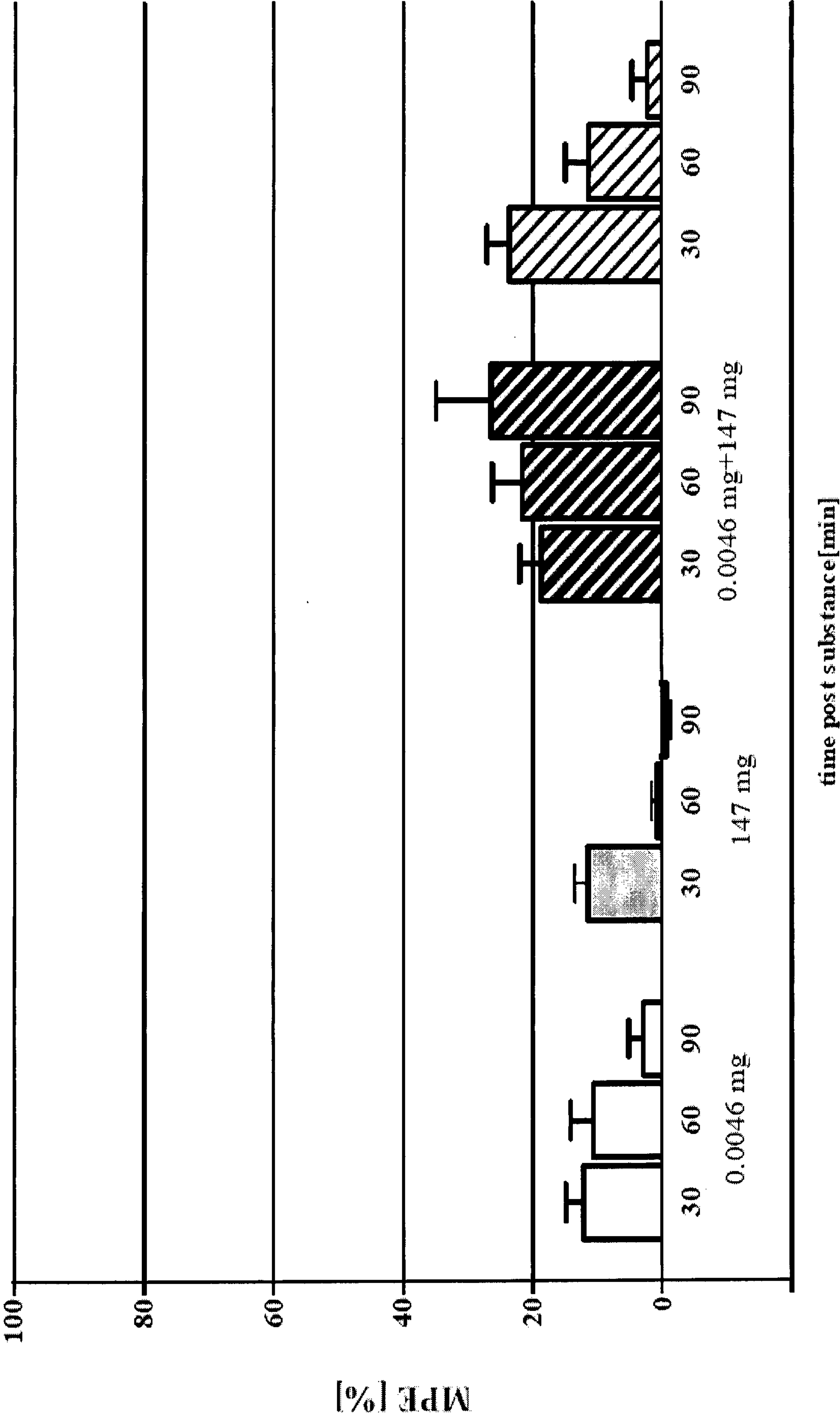


Figure 6

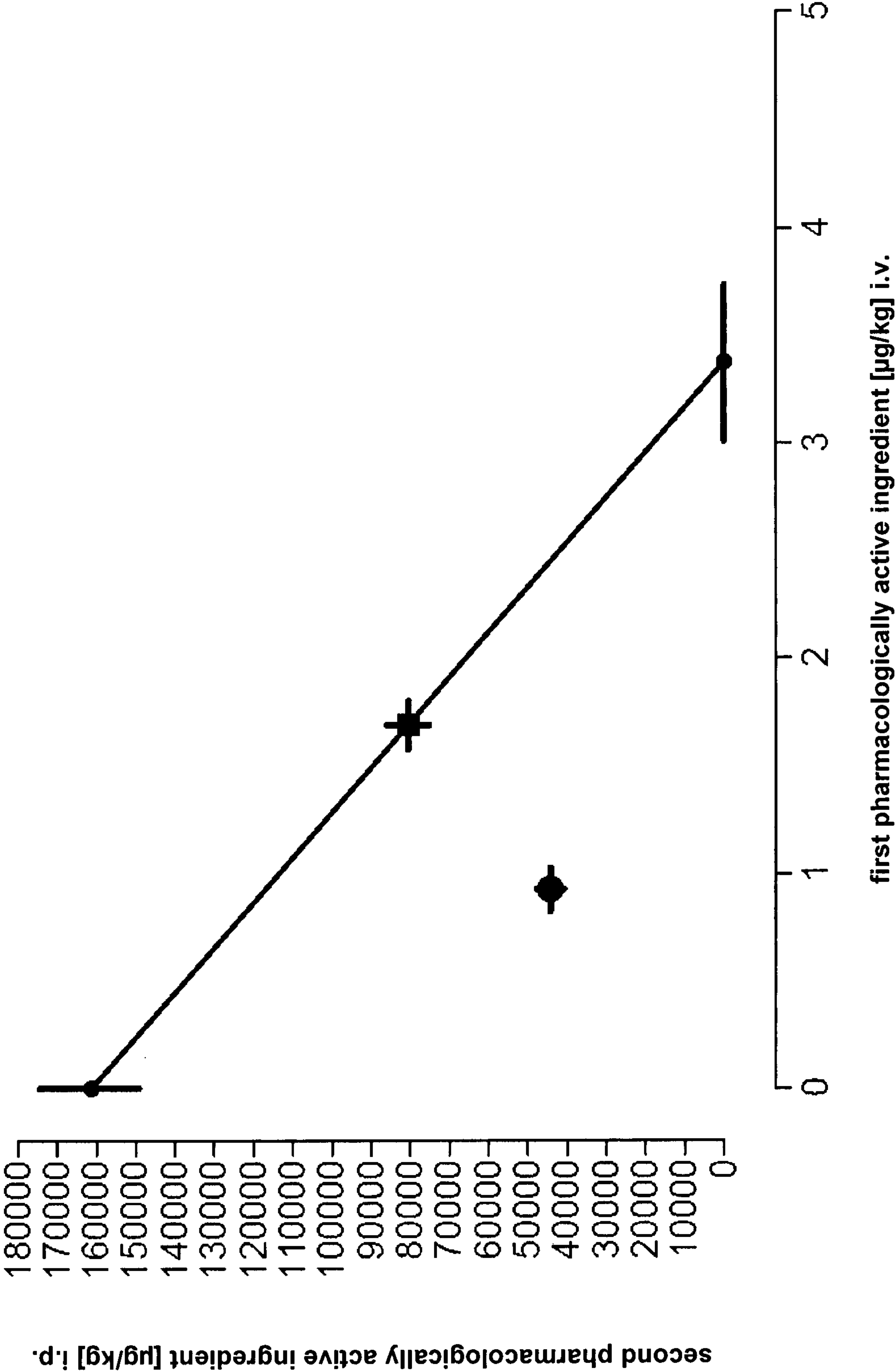


Figure 7

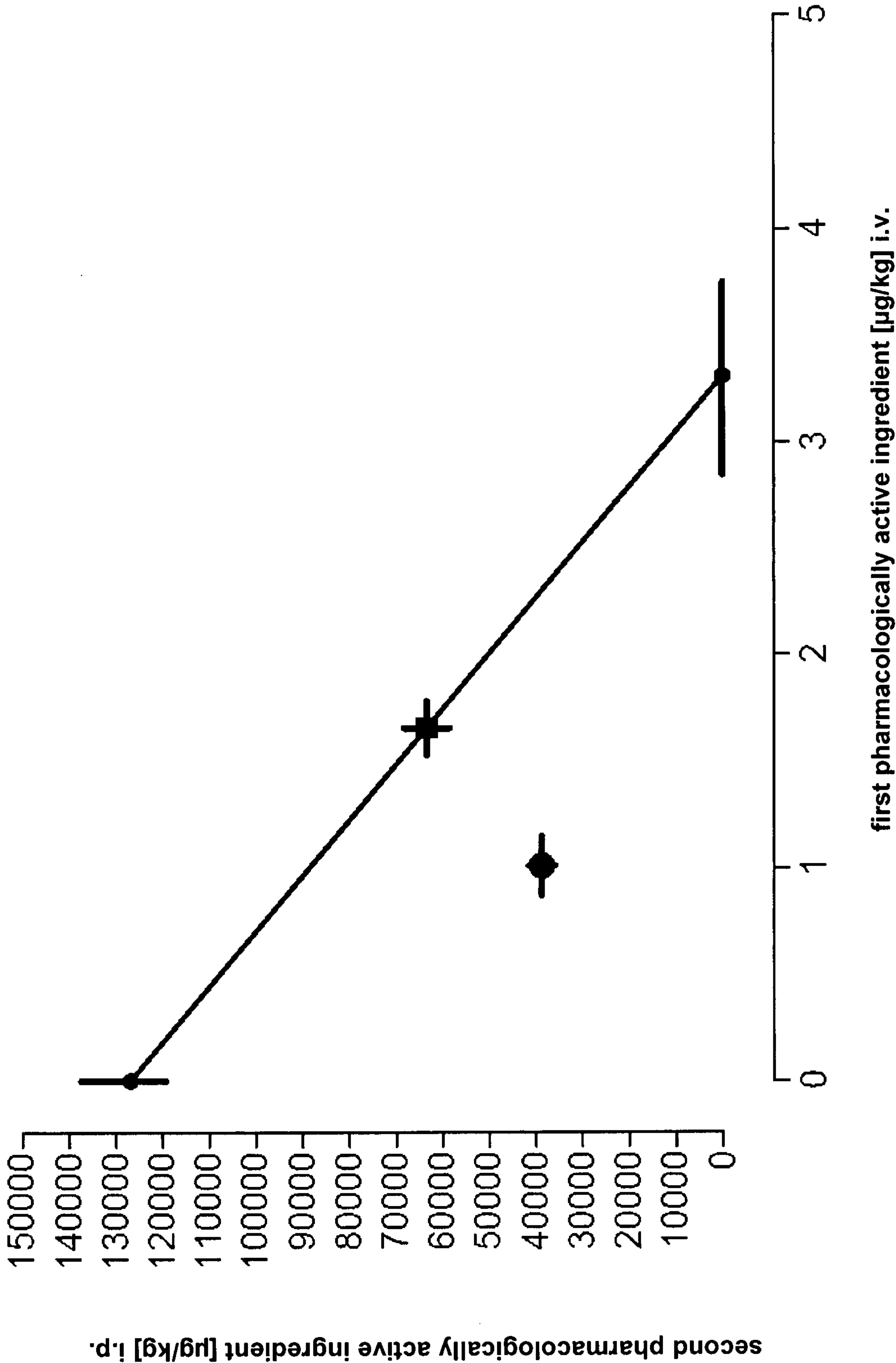


Figure 1

