

ADISINSIGHT (Adis R&D Insight)

Subject Coverage	Weekly reports on new drugs in research, changes in development phases, and licensing availability			
File Type	Substance, Full Text			
Features	Alerts (SDI)	Weekly		
	CAS Registry Number® Identifiers	<input checked="" type="checkbox"/>	Page Images	<input type="checkbox"/>
	Keep & Share	<input checked="" type="checkbox"/>	SLART	<input checked="" type="checkbox"/>
	Learning Database	<input type="checkbox"/>	Structures	<input checked="" type="checkbox"/>
Record Content	<ul style="list-style-type: none"> • Full text reports, i.e., profiles, on drugs in active research and development by the international pharmaceutical industry • Generic names, synonyms, trade names • CAS Registry Numbers® • EphMRA ATC codes, WHO ATC codes • Developing companies, development stages by indication and country • Licensed forecast information from Lehman Brothers • Adis's own unique therapeutic value rating 			
File Size	More than 42,880 records (8/18)			
Coverage	1998 to the present			
Updates	Weekly			
Language	English			
Database Producer	Springer International Publishing AG Copyright Holder			
	Contact Springer Online Services support desk: Email: onlineservice@springer.com Phone: +49 6221 345 4303 (Europe/Asia/Africa) +1 800 777 4643 (North & South America)			
Sources	<ul style="list-style-type: none"> • Direct contact with companies involved with research and development • 1,700 biomedical and medical journals • International meetings and conferences • Company annual reports • News services • Press releases • Licensed Lehman Brothers' PharmaPipelines data 			

User Aids

- Online Helps (HELP DIRECTORY lists all help messages available)
 - STNGUIDE
-

Clusters

- ADISBASES
 - BIOSCIENCE
 - CASRNS
 - COMPANIES
 - FORMULATION
 - FULLTEXT
 - HEALTH
 - MEDICINE
 - PHARMACOLOGY
 - TOXICOLOGY
- [STN Database Clusters](#) information (PDF).
-

Pricing

Enter HELP COST at an arrow prompt (=>).

Search and Display Field Codes

The following fields that allow left truncation (/BI, /CNS and /RNTE) are marked with an asterisk.

Search Field Name	Search Code	Search Examples	Display Codes
Basic Index* (contains single words from the classification code (CC), development status (DSTA), text (TX), revision note (RNTE), company name (CO), chemical name (CN), controlled term (CT), and geographic term (GT) fields, as well as molecular formulas (MF) and CAS Registry Numbers (RN))	None (or /BI)	S IMMUNOSTIMULANTS S ANTI-ATHER? S GLAXO (L) ORIGINATOR S MECHANISM(L)IMMUNOMODULATORS S C (1W) GO S VACCINE# (P) USE S C10H10N2O5 S 47931-85-1	CC, CN, CO, DSTA, MF, RN, RNTE, TX
Accession Number Change Date (1)	/AN /CDAT	S 1998:9493/AN S CDAT>19980100 S JULY 2, 1998/CDAT	AN CDAT
Chemical Name (includes chemical names, generic names, synonyms, and trade names)	/CN	S POLOXAMER 188 NF/CN	CN
Chemical Name Segment*	/CNS	S (METHYL (L) THIAZOL)/CNS S ?AMINOBTYRYL?/CNS S (SALBUTAMOL AND SCHERING)/CNS	CN
Classification Code (EphMRA ATC codes and WHO ATC codes) (code and text) (2)	/CC	S R03/CC S R3/CC S "ANTI-ACNE PREPARATIONS"/CC S TOPICAL PREPARATIONS/CC	CC
Company Name (2) (corporate name and location)	/CO	S SMITHKLINE UNITED KINGDOM/CO S LICENSEE (L) INTROGEN/CO	CO
Controlled Term (indication)	/CT	S ALZHEIMER?/CT S ANXIETY DISORDERS/CT	DSTA
Development Status (development phase, location, and indication)	/DSTA	S (PHASE II (L) GERMANY)/DSTA S (STROKE (L) PRECLINICAL)/DSTA	DSTA
Document Number Element Count, Specific (1)	/DN /Element symbol	S 002345/DN S 1/N AND 3/O	DN MF
Entry Date (1) Field Availability (code and text)	/ED /FA	S L1 AND ED>=19990700 S EVALUATION/FA	Not displayed FA
Geographic Term (code and text)	/GT	S GERMANY/GT S DE/GT	DSTA
Highest Development Phase Journal Title	/HDP /JT	S PHASE III/HDP S ADIS R&D INSIGHT/JT	HDP JT, SO
Molecular Formula	/MF	S C10H10N2O5/MF S C18 H22 N2 O S . CI H/MF	MF
Number of Components (1) Other Source (Adis Alerts Accession Number)	/NC /OS	S L6 AND NC>=2 S "800007351"/OS	MF OS
Periodic Group Reference Revision Date (1)	/PG /RE /RDAT	S T3/PG S JOURNAL OF PHARMACOLOGY/RE S 19980312/RDAT	MF RE RDAT

Search and Display Field Codes (cont'd)

Search Field Name	Search Code	Search Examples	Display Codes
Revision Note* Source Trade Name Update Date (1) Word Count (1)	/RNTE /SO /TN /UP /WC	S PRECLINICAL DEV?/RNTE S ADIS R&D INSIGHT/SO S TANADOPA/TN S L1 AND UP>=19990600 S L1 AND WC	RNTE SO CN Not displayed WC

(1) Numeric search field that may be searched using numeric operators or ranges.

(2) Implied (S) proximity is available in this field.

(3) This score is only available in selected records published in November 2010 and earlier.

DISPLAY and PRINT Formats

Any combination of formats may be used to display or print answers. Multiple codes must be separated by spaces or commas, e.g., D L1 1-5 CN TX. The fields are displayed or printed in the order requested.

Hit-term highlighting is available for all fields except FA, STF, STR, and STS. Highlighting must be ON during SEARCH in order to use the HIT, KWIC, and OCC formats.

Format	Content	Examples
AN CC CDAT (1) CN CO DN DSTA FA (2) HDP JT (2) MF OS RDAT (RNTE) RE RN SO STF STR (3) STS (2,3) TN (2) TX WC	Accession Number Classification Code (EphMRA ATC codes and WHO ATC codes) Change Date Chemical Name (Generic Names, Synonyms, Chemical Name, and Trade Names) (includes TN) Company Name (corporate name and location) (Originator, Parent, Licensee, and Other) Document Number Development Status (development status, location, and indication) Field Availability Highest Development Phase Journal Title Molecular Formula Other Source (Adis Alerts Accession Number) Revision Date and Revision Note Reference CAS Registry Number and Related CAS Registry Number Source Flat Structure (no stereo indicated) Structure Diagram (includes stereo bonds and R/S/E/Z labels when available) Stereo Structure (includes stereo bonds when available) Trade Name Text (Introduction, Evaluation, Commercial Summary (table with Company, Major Markets, Launch Date, Commercial Value, and Patent Expiry), Pharmacology Overview (Mechanism of action, Route of Elimination), Clinical Overview, Adverse Events, Pharmacology (Pharmacokinetics, Clinical Studies), and Therapeutic Trials) (includes EVAL) Word Count	D AN D 1-3 CC D CDAT D CN STR D CO 1,3-5 D AN DN D DSTA D FA D HDP D JT 2 D CN MF D OS D RDAT D RE L1 4 D RN 3,4 D SO D L9 1 3 D L4 STR D STS D TN D TX D WC
ALL (3) DALL (3) IALL (3) IDE (3) IIDE (3) ISTD (3)	AN, SO, DN, CDAT, CN, MF, RN, STR, related RN, CC, HDP, DSTA, CO, OS, WC, TX, RDAT, RNTE, RE ALL, delimited for post-processing ALL, indented with text labels AN, SO, DN, CDAT, CN, MF, RN, STR, related RN, CC, HDP, CO, OS, WC IDE, indented with text labels (IIDE is the default) STD, indented with text labels	D ALL D DALL D IALL D IDE D L2 3 IIDE D D ISTD

DISPLAY and PRINT Formats (cont'd)

Format	Content	Examples
SCAN (1,4) STD (3) TRIAL (1) (SAM, TRI)	CN (Generic Name) (random display, no answer number) AN, SO, DN, CDAT, CN, MF, RN, STR, related RN, CC, HDP, DSTA, CO, OS, WC, TX CN (Generic Name), CDAT	D SCAN D STD D TRIAL TOTAL
HIT KWIC OCC (1)	Fields containing hit terms Hit terms with 20 words on either side (KeyWord-In-Context) Number of occurrences of hit terms and fields in which they occur	D HIT D KWIC NOH D OCC

- (1) No online display fee for this format.
 (2) Custom display format only.
 (3) Stereo structure diagrams are available only on graphics terminals and offline prints.
 (4) SCAN must be entered on the command line, i.e., DISPLAY SCAN, D SCAN.

SELECT, ANALYZE, and SORT Fields

The SELECT command is used to create E-numbers containing terms taken from the specified field in an answer set.

The ANALYZE command is used to create an L-number containing terms taken from the specified field in an answer set.

The SORT command is used to rearrange the search results in either alphabetic or numeric order of the specified field(s).

Field Name	Field Code	ANALYZE/ SELECT (1)	SORT
Accession Number	AN	Y	N
CAS Registry Number	RN	Y (2)	N
CAS Registry Number and Chemical Name	CHEM	Y (3)	N
Change Date	CDAT	Y	Y
Chemical Name	CN	Y (4) (default)	N
	NAME	Y (5)	N
Classification Code (EphMRA and WHO ATC codes)	CC	Y	Y
Company Name (Corporation Name)	CO	Y	Y
Controlled Term (Indication)	CT	Y (6)	N
Development Status	DSTA	Y	N
Document Number	DN	Y	Y
Geographic Term	GT	Y (6)	N
Highest Development Phase	HDP	Y	Y
Journal Title	JT	Y	Y
Molecular Formula	MF	Y	Y
Occurrence Count of Hit Terms	OCC	N	Y
Other Source (Adis Alerts Accession Number)	OS	Y (7)	Y
Reference	RE	Y	N
Revision Date	RDAT	Y (6)	N
Revision Note	RNTE	Y (6)	N
Source	SO	Y	N
Text	TX	Y (8)	N
Trade Name	TN	Y	N
Word Count	WC	N	Y

- (1) HIT may be used to restrict terms extracted to terms that match the search expression used to create the answer set, e.g., SEL HIT CN.
 (2) Selects or analyzes the CAS Registry for the substance and the related CAS Registry Numbers with /BI appended to the terms created by SELECT.

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- (3) Selects or analyzes the CAS Registry for the substance, the related CAS Registry Numbers, Generic Names, Synonyms, Chemical Name, and Trade Names) with /BI appended to the terms created by SELECT.
- (4) Selects or analyzes the Generic Names, Synonyms, Chemical Name, and Trade Names).
- (5) Selects or analyzes the Generic Names, Synonyms, Chemical Name, and Trade Names with /BI appended to the terms created by SELECT.
- (6) SELECT HIT and ANALYZE HIT are not valid with this field.
- (7) Appends /DN to the terms created by SELECT.
- (8) Appends /BI to the terms created by SELECT.

Full-Text Browsing

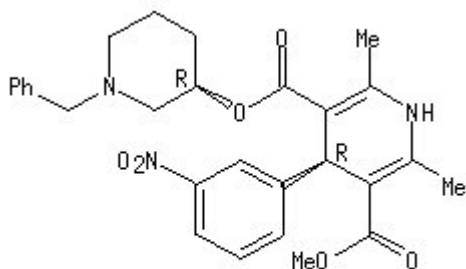
User Request	Example	System Response
DISPLAY BROWSE	=> DISPLAY BROWSE ENTER (L1) OR L#: ENTER (DIS), ANSWER NUMBERS, OR END:	NOVICE version
D BRO Answer number(s) Answer number(s) and format Format only Change default format Forward n fields Backward n fields Search forward for character string Search backward for character string End DISPLAY BROWSE	=> D BRO L1 : :1-3 :4 HIT :TI TX :*KWIC :F3 :B1 :S BONE MARROW :S -NAUSEA :END =>	EXPERT version display answers 1, 2, and 3 in default format display answer 4 in HIT format display title and text of last answer displayed change default to KWIC no answer displayed move forward 3 fields move backward 1 field search forward within record for 'bone marrow' search backward within record for 'nausea' exit DISPLAY BROWSE and return to => prompt

Sample Records

DISPLAY ALL

AN 1998:1 ADISINSIGHT
 SO Adis R&D Insight
 DN 000001
 CDAT Sep 14, 2016
 CN Benidipine
 CN Benidipine hydrochloride; KW 3049; KW3049; Nacadipine; Nakadipine
 CN 3,5-Pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-
 , methyl 1-(phenylmethyl)-3-piperidinyl ester, monohydrochloride,
 (R*,R*)-(+-)-
 CN Caritec(R); Coniel(R)
 MF C28 H31 N3 O6 . Cl H
 RN 91599-74-5
 STR

Relative stereochemistry.



● HCl

RN 105979-17-7 (Benidipine)
 CC EPHMRA ATC CODE: C8A Calcium Antagonists, Plain
 CC WHO ATC CODE: C08C-A Dihydropyridine derivatives
 HDP Launched
 DSTA Launched, China, Angina pectoris
 Launched, India, Angina pectoris
 Launched, Japan, Angina pectoris
 Launched, Philippines, Angina pectoris
 Launched, Turkey, Angina pectoris
 Launched, China, Essential hypertension
 Launched, India, Essential hypertension
 Launched, Japan, Essential hypertension
 Launched, Philippines, Essential hypertension
 Launched, Turkey, Essential hypertension
 Discontinued III, Italy, Angina pectoris
 Discontinued III, Italy, Essential hypertension
 Discontinued II, Germany, Angina pectoris
 Discontinued II, United Kingdom, Angina pectoris
 Discontinued II, United States, Angina pectoris
 Discontinued II, Germany, Essential hypertension
 Discontinued II, United Kingdom, Essential hypertension
 Discontinued II, United States, Essential hypertension
 ORIGINATOR: Kyowa Hakko (Japan)
 PARENT: Kyowa Hakko
 LICENSEE: Bristol-Myers Squibb; Deva Holding; Sun Pharmaceutical
 Industries
 WC 1018
 TX TEXT
 Introduction:

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Company Agreements

In October 2013, Bristol-Myers Squibb licensed the exclusive Chinese marketing rights for benidipine from Kyowa Hakko Kirin. Financial details of the agreement were not disclosed/1/.

Benidipine appears to have been licensed to Deva (an EastPharma subsidiary) for commercialisation in Turkey, and to , Sun Pharmaceutical Industries for commercialisation in India.

Crinos (later Sirton Pharmaceuticals) had licensed benidipine for development in Italy. However, this agreement no longer appears to be active.

In March 2015, Sun Pharmaceutical Industries acquired Ranbaxy/2/.

Introduction

Benidipine is an orally bioavailable dihydropyridine antagonist of L-type, N-type and T-type calcium channels. The drug was developed by Kyowa Hakko (now Kyowa Hakko Kirin) for the treatment of essential hypertension and angina pectoris, and gained approval in Japan in 1991. It has subsequently been launched in Japan, China, Philippines and Turkey (as Coniel sup((R))), and in India (as Caritec sup((R))) for these indications.

In October 2008, Kyowa Hakko merged with Kirin Pharma to form Kyowa Hakko Kirin/3/.

Generic versions of Coniel sup((R)) were launched in Japan in July 2006, following expiry of patent protection in the region.

Key Development Milestones

Benidipine was approved in China in September 2008 for the treatment of angina pectoris, following the filing of an application for regulatory approval in 2007/4/. The drug had been launched in China for the treatment of hypertension in December 2004, after gaining regulatory approval in March 2004. Kyowa Hakko had launched benidipine in the Philippines for both indications by April 2002.

In July 2006, Deva was granted marketing authorisation for benidipine in angina pectoris and essential hypertension, and subsequently launched the product in that country during 2007. Ranbaxy launched the drug in India, in October 2000.

Kyowa Hakko announced in its 2003 annual report that a special investigation evaluating the efficacy and safety of long-term (1 year) administration of benidipine in 10 000 older patients with hypertension had been initiated. A second large-scale clinical trial in collaboration with Yamaguchi University had also been initiated to investigate benidipine in combination with one of three types of antihypertensives (beta-blockers, angiotensin II receptor blockers and antihypertensive diuretics) over a three-year period (COPE; NCT00135551). The effectiveness and safety of the three combination regimens was to be compared and evaluated. This trial enrolled 3501 patients with hypertension in Japan, and was completed in November 2010.

Benidipine was undergoing phase III clinical trials in Italy and phase II trials in Germany, the United Kingdom and the USA for angina pectoris and essential hypertension. However, development appears to have been discontinued in these countries.

TX PHARMACOLOGY OVERVIEW:

Pharmacodynamics:

Coronary and cerebral vasodilatory effects in vivo; marked BP-lowering effects; diuresis; natriuresis

Mechanism of action:

L-type calcium channel antagonists

L-type calcium channel modulators

Calcium channel antagonists

Calcium channel modulators

- Ion channel antagonists
- Ion channel modulators
 - Membrane glycoprotein inhibitors
 - Membrane transport protein inhibitors
 - Membrane glycoprotein modulators
 - Membrane transport protein modulators
 - Glycoprotein inhibitors
 - Membrane protein inhibitors
 - Carrier protein inhibitors
 - Glycoprotein modulators
 - Membrane protein modulators
 - Carrier protein modulators
 - Protein inhibitors
 - Glycoconjugate inhibitors
 - Glycoconjugate modulators
 - Protein modulators
 - Carbohydrate metabolism inhibitors
- Carbohydrate metabolism modulators
- N type calcium channel antagonists
- N-type calcium channel modulators
- Calcium channel antagonists
- Calcium channel modulators
- Ion channel antagonists
- Ion channel modulators
 - Membrane glycoprotein inhibitors
 - Membrane transport protein inhibitors
 - Membrane glycoprotein modulators
 - Membrane transport protein modulators
 - Glycoprotein inhibitors
 - Membrane protein inhibitors
 - Carrier protein inhibitors
 - Glycoprotein modulators
 - Membrane protein modulators
 - Carrier protein modulators
 - Protein inhibitors
 - Glycoconjugate inhibitors
 - Glycoconjugate modulators
 - Protein modulators
 - Carbohydrate metabolism inhibitors
- Carbohydrate metabolism modulators
- T type calcium channel antagonists
- T-type calcium channel modulators
- Calcium channel antagonists
- Calcium channel modulators
- Ion channel antagonists
- Ion channel modulators
 - Membrane glycoprotein inhibitors
 - Membrane transport protein inhibitors
 - Membrane glycoprotein modulators
 - Membrane transport protein modulators
 - Glycoprotein inhibitors
 - Membrane protein inhibitors
 - Carrier protein inhibitors
 - Glycoprotein modulators
 - Membrane protein modulators
 - Carrier protein modulators
 - Protein inhibitors
 - Glycoconjugate inhibitors
 - Glycoconjugate modulators
 - Protein modulators
 - Carbohydrate metabolism inhibitors
- Carbohydrate metabolism modulators
- Activity versus parent drug: unspecified parent

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TX CLINICAL OVERVIEW:

Route(s) of Administration: PO

Adverse events:

rare: Diarrhoea, Oedema.

Drug Interactions:

Unknown.

TX Adverse Events:

In 55 patients with essential hypertension receiving benidipine 2-8 mg/day for \leq 1 year, adverse events included lightheadedness (n = 1), diarrhoea (1) and peripheral oedema (1)/5/.

TX PHARMACOLOGY:

Pharmacodynamics (Hypertension):

Preclinical studies: the long term effects of ceronapril 40 mg/kg/day, AE 0047 20 mg/kg/day and benidipine 10 or 20 mg/kg/day were examined in stroke-prone spontaneously hypertensive rats. In treated rats, the incidence of cerebrovascular lesions was significantly depressed and their life-spans were extended compared to the untreated control rats. AE 0047 sustained BP under 210mm Hg without developing fibrinoid deposition on arterial walls. After benidipine, thickened arterial walls were observed and BP remained over 250mm Hg. In contrast to benidipine, ceronapril reduced the occurrence of smooth muscle proliferation and BP levels were similar to those of benidipine/6/.

Clinical studies: a randomised, single-blind, crossover study in 15 salt-sensitive patients with essential hypertension assessed the efficacy of benidipine and controlled release nifedipine on sodium-induced changes in systemic and regional haemodynamics. Oral benidipine 4-8 mg/day once daily for 73 days significantly reduced MAP and increased CI, superior mesenteric blood flow and renal blood flow during low and high sodium intake. Nifedipine 10-30 mg/day also significantly reduced MAP during low sodium intake, but had no effects on HR, CI or regional blood flow. The high sodium diet increased MAP, CI and terminal aortic flow (all $p < 0.05$), and reduced mesenteric and renal blood flows ($p < 0.05$) during nifedipine administration/7/.

In 15 patients with essential hypertension, benidipine 4 mg/day and trandolapril 1 mg/day for 12 weeks similarly decreased BP, and increased concentrations of nitrite/nitrate (NOx) and cGMP. Neither agent affected HR, lipid profiles and renal functions/8/.

In 10 elderly patients with essential hypertension undergoing mental arithmetic test, administration of oral benidipine 4mg od for 12 weeks significantly decreased 24-h BP, and had no marked effect on HR. However, the decrease in night-time DBP was not significant, and the decrease in night-time SBP was minimal. In benidipine recipients, the increase in SBP induced by mental arithmetic test was significantly decreased compared with baseline/9/.

Pharmacodynamics (Ischaemic Heart Disease):

Benidipine suppresses ischaemic ECG changes and attenuates ST and T wave elevation in animal models. Mild and long lasting dose-dependent increases in coronary sinus outflow and decreases in BP are seen at doses > 1 microg/kg IV. Benidipine protects the ischaemic canine myocardium and maintains global cardiohaemodynamics. Other animal studies have shown that benidipine exhibits preferential coronary and cerebral vasodilating activity, and has a longer duration of action than nifedipine or nicardipine.

TX THERAPEUTIC TRIALS:

Hypertension:

In patients with essential hypertension (n = 21), oral once daily benidipine 4 mg/day for 2 weeks produced a long lasting reduction in BP

compared with baseline/10/.

In an open, multicentre study in 78 patients with essential hypertension, monotherapy with oral benidipine 2-8 mg/day od for <= 1 year significantly decreased BP from baseline. Similar effect was achieved when benidipine was used in combination with other antihypertensive agents (n = 19) (details not provided). 42% of patients in the benidipine monotherapy group and 44% of patients in the combination therapy group had their BP normalised at 1 year (BP < 150/90mm Hg)/5/.

In a randomised study in 86 patients with essential hypertension, beta-blockers arotinolol, bisoprolol, ACE inhibitors captopril, imidapril and calcium antagonists nisoldipine and benidipine for 12 weeks significantly and similarly decreased 24h ambulatory BP. 24h HR decreased significantly with the beta-blockers arotinolol and bisoprolol. There were no differences in circadian and ultradian variations among the major first, second and third peaks of SBP, DBP and HR in patients receiving beta-blockers or ACE inhibitors. Calcium antagonists shortened the periodicity of ultradian variations in second and third peaks of SBP/11//9/.

RDAT	RNTE
30 Oct 2000	Launched for Angina pectoris in India (PO)
30 Oct 2000	Launched for Essential hypertension in India (PO)
26 Jan 2000	Two studies have been added to the Hypertension therapeutic trials section (720623, 746001)
05 Jul 1999	Registered for Angina pectoris in India (PO)
05 Jul 1999	Registered for Essential hypertension in India (PO)
30 Apr 1999	A study has been added to the Hypertension pharmacodynamics section (746001)
29 Sep 1998	A study has been added to the Hypertension pharmacodynamics section (691650)
11 Nov 1994	A preclinical study has been added to the hypertension pharmacodynamics section (307950)
14 Sep 1994	New profile

- RE
1. Bristol-Myers Squibb. Bristol-Myers Squibb Signs Licensing Agreement for Coniel (benidipine) in China. Media Release. : 22 Oct 2013. Available from: URL: <http://www.bms.com.cn>. (English).
 2. Sun Pharmaceutical Industries. Sun Pharma announces closure of merger deal with Ranbaxy. Media Release. : 25 Mar 2015. Available from: URL: <http://www.sunpharma.com>. (English).
 3. Kyowa Hakko Kogyo Co Ltd, Kirin Pharma Company Limited, et al. Strategic Alliance Between Kyowa Hakko Group and Kirin Group Maximizing Synergy Through an Alliance Centered Around the Pharmaceutical Business. Media Release. :22 Oct 2007. Available from: URL: <http://www.kyowa.co.jp>. (English).
 4. Kyowa Hakko Kogyo Co Ltd. Kyowa Hakko Interim Operating Income up 25.2%. Media Release. : 29 Oct 2007. Available from: URL: <http://www.kyowa.co.jp>. (English).
 5. Imazu M, Yamabe T, et al. Antihypertensive effects and safety of long-term treatment with benidipine hydrochloride in essential hypertensive patients. Shinryo to Shinyaku. 32: 995-1005, 1995. (Japanese).
 6. Ohta Y, Chikugo T, et al. Long term therapeutic effects of ACE inhibitor and calcium antagonists on hypertensive vascular lesions in M-SHRSP. Clinical and Experimental Pharmacology and Physiology. (Suppl. 1): 103, 1994. (English).
 7. Shimamoto H, Shimamoto Y. Benidipine counteracts sodium-induced alterations in systemic and regional hemodynamics. Blood Pressure. 6: 18-23, Jan 1997. (English).
 8. Takase H, Sugiyama M, et al. Effect of antihypertensive therapy with benidipine or trandolapril on serum nitrite/nitrate levels in essential hypertension. Journal of Hypertension. 16 (Suppl. 2): 99, Jun 1998. (English).
 9. Muneta S, Kohara K, et al. Effects of benidipine hydrochloride on

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- 24-hour blood pressure and blood pressure response to mental stress in elderly patients with essential hypertension. *International Journal of Clinical Pharmacology and Therapeutics*. 37: 141-147, Mar 1999. (English).
10. Nakanishi T, Takahashi H, et al. Effects of benidipine hydrochloride on 24-hour blood pressure. *Current Therapeutic Research - Clinical and Experimental*. 53: 270-276, Mar 1993. (English).
 11. Kawamura H, Mitsubayashi H, et al. Calcium channel blockers shorten the periodicity of ultradian variation in blood pressure in patients with essential hypertension. *Koketsuatsu*. 21: 179-186, Sep 1998. (English).

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