Drugs of the Future 1999, 24(4): 367-374

CCC: 0377-8282/99

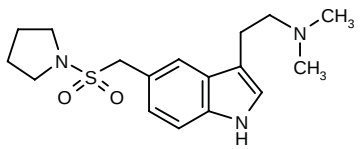
Almotriptan

Prop INN; USAN

Antimigraine
5-HT$_{1D/1B}$ Agonist

LAS-31416

3-[2-(Dimethylamino)ethyl]-5-(pyrrolidin-1-ylsulfonylmethyl)-1*H*-indole



$C_{17}H_{25}N_3O_2S$ Mol wt: 335.4720

CAS: 154323-57-6

EN: 208489

Synthesis

Almotriptan has been obtained by several related ways:

1) The hydrolysis of 4-chlorobutyraldehyde dimethylacetal (I) with HCl gives the corresponding aldehyde (II), which is condensed with 4-(1-pyrrolidinylsulfonylmethyl)-phenylhydrazine (III) by means of HCl in methanol/water, giving 3-(2-aminoethyl)-5-(1-pyrrolidinylsulfonylmethyl)-1*H*-indole (IV). Finally, this compound is methylated with formaldehyde and $NaBH_4$ in methanol (1, 2). Scheme 1.

2) The direct condensation of 4-chlorobutyraldehyde dimethylacetal (I) with 4-(1-pyrrolidinylsulfonylmethyl)-phenylhydrazine (III) by means of HCl in water also yields intermediate 3-(2-aminoethyl)-5-(1-pyrrolidinylsulfonylmethyl)-1*H*-indole (IV) (1, 2). Scheme 1.

3) The decarboxylation of 3-[2-(dimethylamino)ethyl]-5-(1-pyrrolidinylsulfonylmethyl)-1*H*-indole-2-carboxylic acid (V) catalyzed by means of Cu_2O in quinoline at 190 °C also gives almotriptan (3, 4). Scheme 1.

4) The intermediate 4-(1-pyrrolidinylsulfonylmethyl)-phenylhydrazine (III) can be obtained as follows: The condensation of pyrrolidine (VI) with 1-(4-nitrobenzylsulfonyl)chloride (VII) in dichloromethane gives the expected sulfonamide (VIII), which is reduced with H_2 over RaNi in DMF, yielding 4-(1-pyrrolidinylsulfonylmethyl)aniline (IX). The diazotation of (IX) with $NaNO_2$/HCl affords the corresponding diazo compound (X), which is finally reduced to the target intermediate (III) with $SnCl_2$/HCl (2). Scheme 2.

Description

Amorphous solid, acid D,L-malate, m.p. 169-71 °C (1); hydrochloride, m.p. 218-20 °C (3, 4).

Introduction

Several theories have been proposed for the etiology of migraine (5). The vasodilatatory theory suggests that extracranial vasodilatation during an attack is the cause of headache, the neurological theory proposes that migraine is the result of abnormal firing in brain neurons and the inflammatory theory suggests that the dural membrane surrounding the brain becomes inflamed and hypersensitive due to the release of neuropeptides from primary sensory nerve terminals. Other theories support the role of substance P, calcitonin gene-related peptide (CGRP) and nitric oxide in the etiology of a migraine attack.

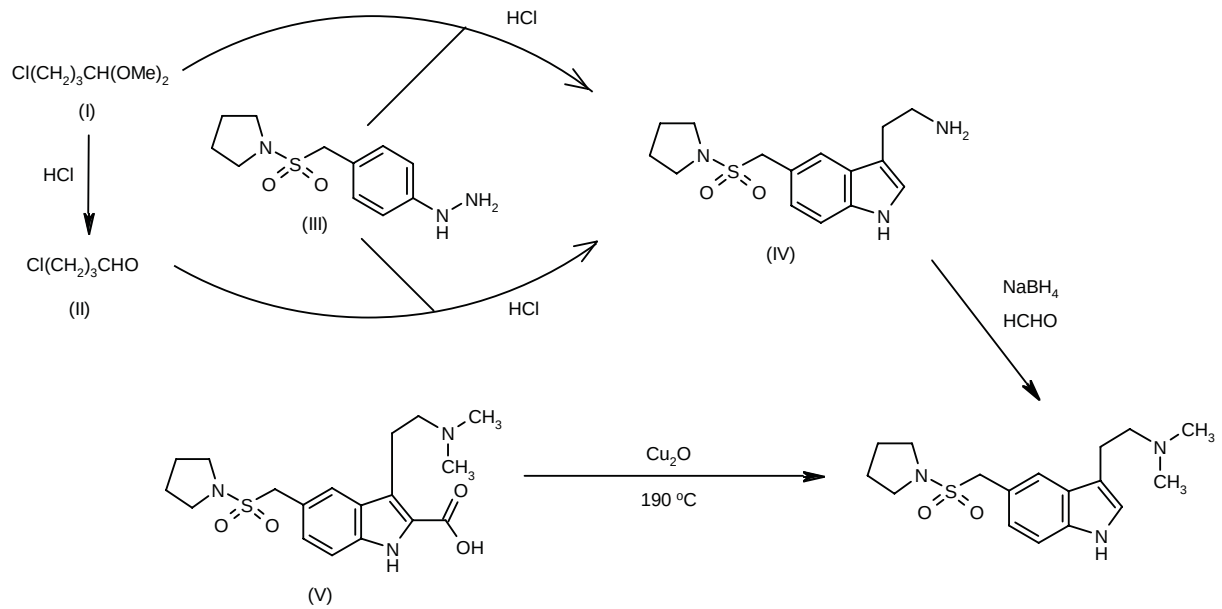
Based on these hypotheses, several classes of compounds have been investigated as antimigraine agents, including tachykinin NK_1 receptor antagonists, endothelin receptor antagonists, calcium channel blockers, histamine H_3 receptor agonists, $GABA_A$ receptor modulators and serotonin 5-$HT_{1B/1D}$ and 5-HT_{1F} receptor agonists. The structures of nonserotonergic compounds and serotonin receptor agonists currently under investigation as antimigraine agents are shown in Table I and Table II, respectively.

The observation of the increased excretion of serotonin and 5-hydroxyindoleacetic acid (a metabolite of serotonin) during the headache phase of a migraine attack and the demonstration that migraine could be experimentally induced through serotonin depletion and alleviated with injected serotonin has supported the hypothesis that serotonin is the main mediator in the migraine syndrome.

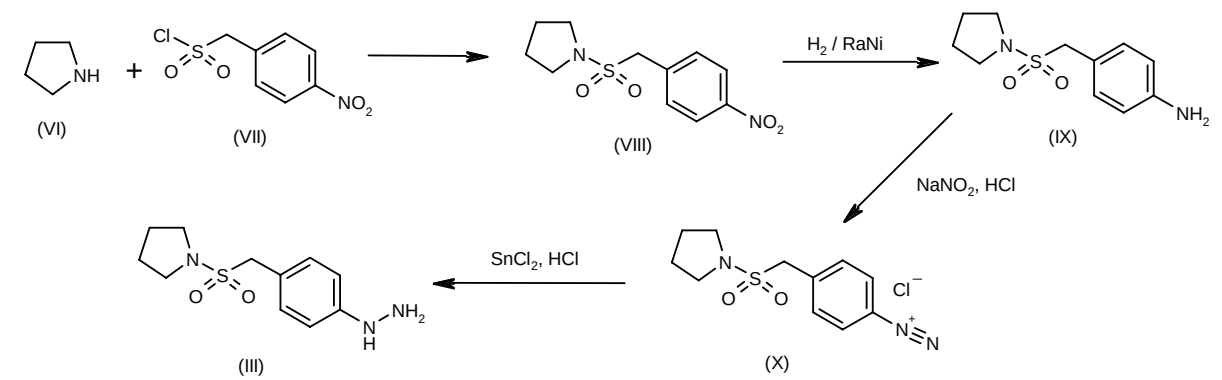
Serotonin acts through a family of receptors, including 5-HT_1, 5-HT_2, 5-HT_3, 5-HT_4, 5-HT_5, 5-HT_6 and 5-HT_7. The

J.M. Palacios[1], X. Rabasseda[2], J. Castañer[2]. [1]Almirall Prodesfarma S.A., Cardener 68-74, 08024 Barcelona and [2]Prous Science, P.O. Box 540, 08080 Barcelona, Spain.

Scheme 1: Synthesis of Almotriptan



Scheme 2: Synthesis of Intemediate (III)



5-HT_1 receptor family comprises five different receptors (5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E} and 5-HT_{1F}) that couple to protein $G_{i/o}$ to inhibit cAMP formation. 5-HT_{1B} and 5-HT_{1D} receptors are unambiguously discriminated in most animal species; only in rodents can they be pharmacologically differentiated. 5-HT_{1B}, 5-HT_{1D} and 5-HT_{1F} have been involved in the etiology of migraine headache attacks.

The development of serotonin 5-$HT_{1B/1D}$ receptor agonists has opened a new era in the treatment of migraine and has dramatically increased the response rates of patients in comparison with previously available treatments (mainly ergot alkaloids).

Serotonin 5-$HT_{1B/1D}$ agonists, generically called triptans, are currently the most extensively studied class of antimigraine drugs. Four of them are currently in use (sumatriptan, naratriptan, rizatriptan and zolmitriptan), and others are in development. Almotriptan is a new 5-$HT_{1B/1D}$ agonist in advanced testing as a therapy for migraine headache.

Table I: Nonserotonergic compounds under investigation as antimigraine agents (from Prous Science Ensemble database).

NK_1 receptor antagonists

1. Lanepitant
   Phase II (Lilly)
2. L-758298
   Clinical (Merck & Co.)

H_3 receptor agonists

3. SCH-50971
   Preclinical (Schering-Plough)

Calcium channel blockers

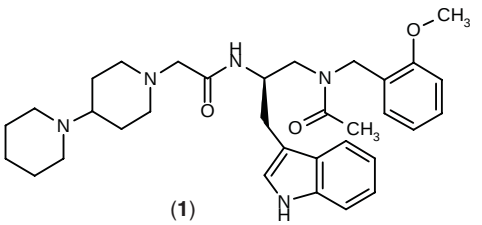
4. Lomerizine HCl
   Preregistered (Kanebo)
5. Dotarizine
   Preregistered (Ferrer)

$GABA_A$ receptor moduators

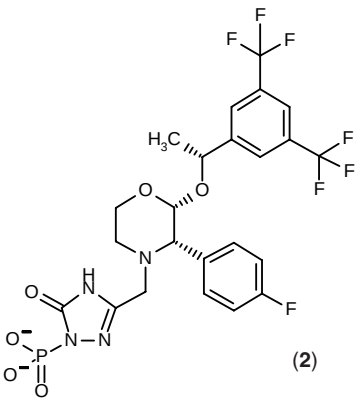
6. Ganaxolone
   Phase II (CoCensys)

Other mechanisms

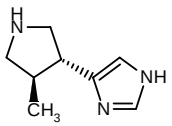
7. SB-220453
   Phase II (SmithKline Beecham)



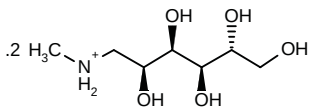
(**1**)

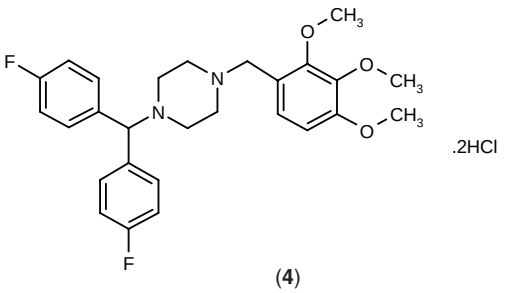


(**2**)

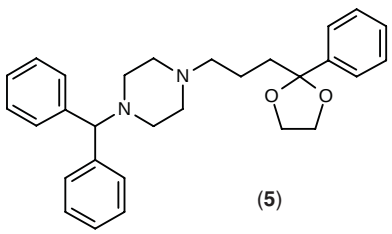


(**3**)

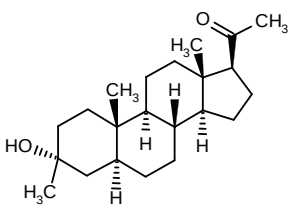




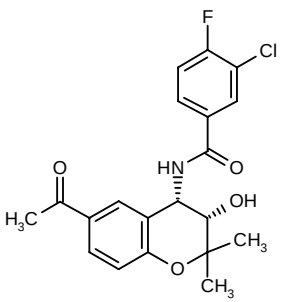
(**4**)



(**5**)



(**6**)



(**7**)

Pharmacological Actions

Migraine appears to involve a combination of cranial vasodilatation, peripheral trigeminal nerve activation and consequent excitation of trigeminal neurons within the trigeminocervical complex (caudal brainstem and upper cervical spinal cord). The triptans act by inducing vasoconstriction of cranial vessels through activation of $5\text{-}HT_{1B}$ receptors and/or by inhibiting neuronal traffic across the trigeminal nerve, which innervates the vessels and the pain-producing dura mater, through $5\text{-}HT_{1D}$ receptors.

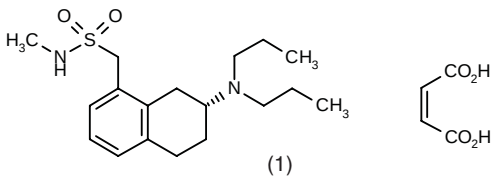
Table II: Serotonin receptor agonists under investigation as antimigraine agents (from Prous Science Ensemble database).

5-HT$_{1B/1D}$ receptor agonists

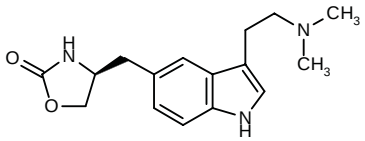
1. MDL-747216
   Preclinical
   (Hoechst Marion Roussel)
2. Zolmitriptan
   Launched-1997 (Zeneca)
3. Almotriptan
   Phase III (Almirall Prodesfarma)
4. Frovatriptan
   Preregistered
   (Vanguard Medica; Elan)
5. IS-159
   Phase II (Immunotech)
6. Naratriptan
   Launched-1997 (Glaxo Wellcome)
7. Rizatriptan benzoate
   Launched-1998 (Merck & Co.)
8. PNU-109291
   Preclinical (Pharmacia & Upjohn)
9. Eletriptan
   Preregistered (Pfizer)
10. L-775606
    Preclinical (Merck & Co.)
11. Sumatriptan succinate
    Launched-1991 (Glaxo Wellcome)
12. F-11356
    Preclinical (Pierre Fabre)
13. Sumatriptan dimer
    Preclinical (Pierre Fabre)

5-HT$_{1F}$ receptor agonists

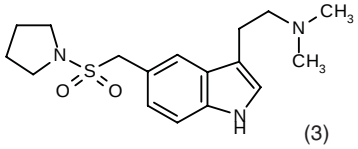
14. LY-344864
    Preclinical (Lilly)
15. LY-334370
    (Lilly; Synaptic)
    Recently discontinued



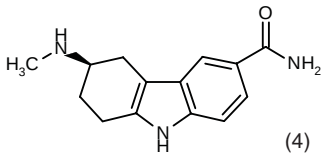
(1)



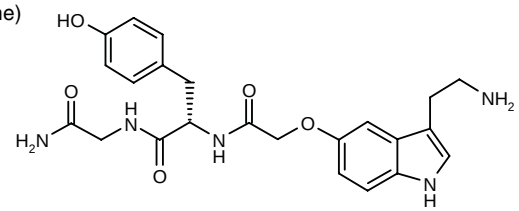
(2)



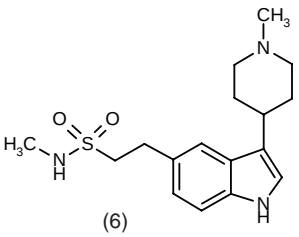
(3)



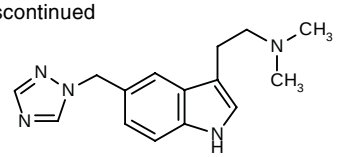
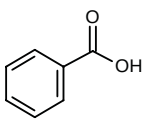
(4)



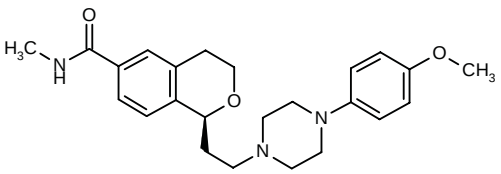
(5)



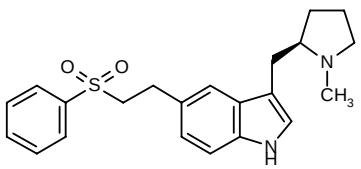
(6)

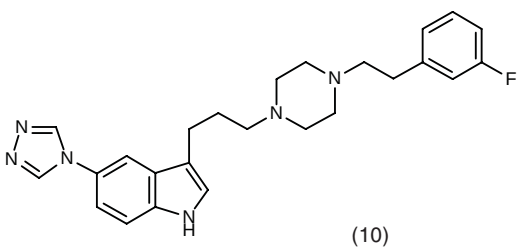
(7)



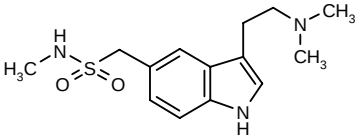
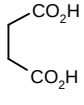
(8)



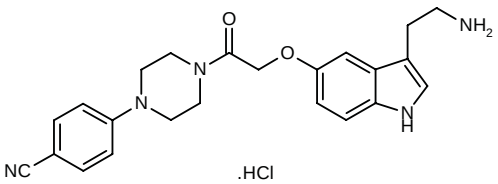
(9)



(10)

(11)

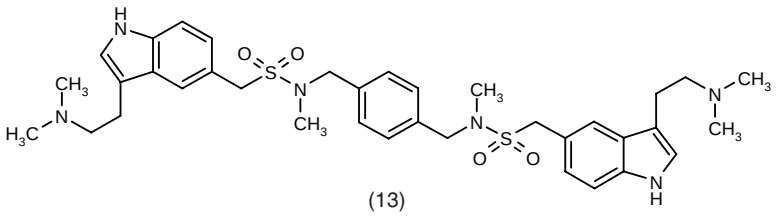


.HCl

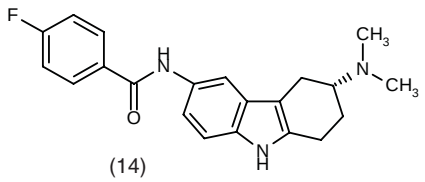
(12)

(Continued)

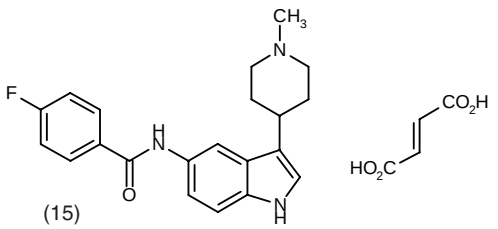
Table II: Serotonin receptor agonists under investigation as antimigraine agents (continued).



(13)



(14)



(15)

Table III: General pharmacological properties of almotriptan (6, 7).

Test	Material/Method	Result
Vasoconstriction, induction	Vein (saphenous), dog	EC_{50} = 0.39 μM
	Artery (meningeal), pig	EC_{100} = 1.6 μM
	Artery (meningeal), human	EC_{50} = 0.03 μM
	Artery (temporal), human	EC_{50} = 0.7 μM
	Artery (renal), pig	EC_{50} > 100 μM
	Artery (renal), rabbit	EC_{50} > 100 μM
	Artery (mesenteric), rabbit	tEC_{50} > 100 μM
	Artery (basilar), human	EC_{50} = 3.5 μM
	Artery (pulmonary), human	EC_{50} > 10 μM
Cardiodepression, induction	Heart, guinea pig	IC_{50} > 10 μM
Capillary hyperpermeability (electrically induced), inhibition	Dura mater, guinea pig	ED_{50} = 200 μg/kg i.v.
Carotid resistance increase, induction	Cats (anesthetized)	ED_{100} = 11 μg/kg i.v.

Almotriptan is a selective 5-$HT_{1B/1D}$ receptor agonist which shows high and specific affinity for 5-$HT_{1B/1D}$ receptors in cranial vessels, but poor affinity for receptors in peripheral arteries. Affinity for 5-HT_{1A} and 5-HT_7 receptors was 35-51 times lower than for 5-$HT_{1B/1D}$ receptors, while affinity for most nonserotonergic receptors was negligible (K_i >1 μM) (6).

Almotriptan exhibited less spasmogenic effects on coronary arteries than other 5-$HT_{1B/1D}$ agonists such as sumatriptan. In a functional affinity assay in isolated dog saphenous vein, almotriptan elicited concentration-dependent contractions, with an EC_{50} value of 390 nM. Similarly, infusion of almotriptan into the porcine meningeal vasculature induced vasoconstriction, with an EC_{100} value of 1.6 μM, whereas in human meningeal and temporal arteries it was active at EC_{50} values of 30 and 700 nM, respectively. In guinea pig dura mater, the drug inhibited electrically induced capillary hyperpermeability with an ED_{50} of 0.2 mg/kg i.v. (7).

Almotriptan is highly vascular-selective, and was ineffective or much less active in pig and rabbit renal arteries and rabbit mesenteric arteries (EC_{50} >100 mM) than in human basilar and pulmonary arteries (EC_{50} = 3.5 and >10 μM, respectively. In guinea pig hearts it was not cardiodepressant (IC_{50} > 10 μM) (6, 7).

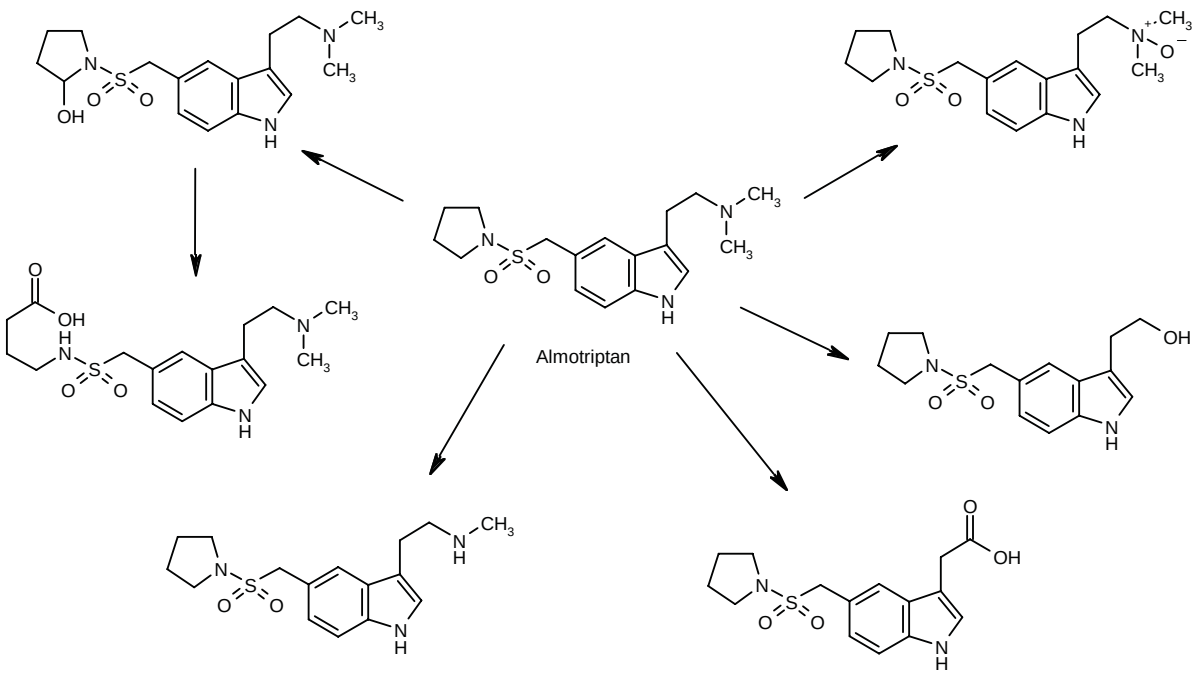
In studies in mice, almotriptan did not induce behavioral toxicity at doses up to 300 mg/kg p.o. and no fatal acute toxicity was observed in animals treated with doses up to 2000 mg/kg p.o. (6, 7).

The basic pharmacological properties of almotriptan are summarized in Table III.

Pharmacokinetics and Metabolism

Almotriptan has high absolute oral bioavailability (70%), one of the highest within the triptan class of compounds, with similar pharmacokinetic profiles in men and women. In healthy volunteers, almotriptan exhibited linear pharmacokinetics. Peak plasma concentrations (C_{max}) after 12.5, 25 or 50 mg almotriptan ranged from 49.5 ng/ml with the lowest dose to 213.5 ng/ml with the highest dose. C_{max} and area under the plasma concentration curve (AUC) after oral doses of 200 mg were 565 ng/ml

Scheme 3: Metabolism of Almotriptan



and 3833.3 ng´h/ml, respectively. Time to C_{max} (t_{max}) was constant across the entire dosing range (1.5-3.8 h). The pharmacokinetics and bioavailability of almotriptan were not affected by food (8, 9).

Almotriptan is predominantly cleared by the kidneys as unaltered drug (45%) or metabolized 45% by MAO-A and liver, mainly through the CYP3A cytochrome family to inactive metabolites, with a half-life ($t_{½}$) of 3.0-3.7 h. All the metabolites are excreted mainly by urine. *In vitro* in liver microsomes, almotriptan is converted into 5 different metabolites (Scheme 3). However, only two phase 1 metabolites have been detected *in vivo* in human urine: the γ-aminobutyric acid and indoleacetic acid derivatives (10). Following oral doses of 5 and 10 mg, 27% of the dose was recovered in urine as unchanged compound over 12 h, a percentage that increased to 35-40% after doses of 25-200 mg p.o. However, no dose modification was deemed necessary in patients with any degree of renal impairment.

Adjustment of almotriptan dose is not necessary in patients with mild or moderate renal impairment. However, those with severe renal impairment should take only one 12.5 mg tablet in a 24-h period.

Clinical Studies

Data from clinical trials with almotriptan indicate a therapeutic dose of 12.5 mg, which achieved a rapid onset of action (30 min) and was significantly more effective than placebo. With this dose, a significant proportion of patients were pain-free at 1 h postdosing and at 2 h, response rates were equivalent to the hightest rates obtained with other antimigraine compounds. Preliminary data from an open, long-term study indicates that almotriptan is consistently effective across and within patients, with response rates in excess of 84% for 13,751 attacks in 762 patients. Furthermore, if and when a second dose was required, it was both effective and safe. Almotriptan was also effective in the relief of migraine-associated symptoms, which resolved with the headache.

The results of a randomized, double-blind, placebo-controlled clinical trial in 908 migraine patients have been reported. Patients received single doses of 6.25 or 12.5 mg of almotriptan or placebo, and headache relief at 2 h was reported in 55, 65 and 32% of the patients, respectively. The highest dose was determined to have the optimum efficacy-tolerability ratio for use in the acute relief of migraine headache (11) (Box 1).

In a placebo-controlled trial in 169 patients with migraine, almotriptan elicited significant responses in 80, 70 and 86% of patients after doses of 25, 100 and 150 mg, respectively, as compared with 66 and 42% for 5 mg almotriptan and placebo, respectively. Favorable efficacy was reported in terms of reduction of headache after 1 h, freedom from pain at 1 and 2 h, reduction in escape medication requirements, shortening of migraine attack, relief of nausea, vomiting, photophobia and phonophobia, and

Box 1: Efficacy and tolerability of almotriptan in patients with migraine (11).

Design	Randomized, placebo-controlled clinical trial
Population	Patients with migraine according to the criteria of the International Headache Society (n = 908)
Treatments	Almotriptan (A), 6.25 or 12.5 mg Placebo (P)
Results	Headache relief at 2 h, A12.5 (65%) > A6.25 (55%) > P (32%)
Adverse events	A12.5 (18%) = A6.25 (13%) = P (16%)

Box 2: Efficacy of almotriptan in patients with migraine (12, 13).

Design	Randomized, dose-finding, placebo-controlled clinical trial
Population	Patients with migraine (n = 169)
Treatments	Almotriptan (A), 5, 25, 100 or 150 mg p.o. Placebo (P)
Results	Response rate, A150 (86%) $\geq$ A25 (80%) $\geq$ A100 (70%) > A5 (66%) $\geq$ P (42%)
Adverse events	A150 $\geq$ A100 > A25 = A5 = P (no serious AEs occurred)

Box 3: Efficacy of almotriptan compared to sumatriptan in patients with migraine (14).

Design	Randomized, placebo-controlled clinical trial
Population	Patients with migraine (n = 668)
Treatments	Almotriptan (A), 12.5 and 25 mg p.o. (n = 375) Sumatriptan (S), 100 mg p.o. (n = 194) Placebo (P) (n = 99)
Results	Pain relief at 2 h: S (64%) $\geq$ A12.5 (60%) = A25 (58%) > P (42%)
Recurrence rate	A25 (15%) $\leq$ A12.5 (18%) < S (25%) $\geq$ P (20%)

reduction in the frequency of migraine recurrences (12, 13) (Box 2).

The antimigraine efficacy of almotriptan (12.5 and 25 mg p.o.) was found to be equivalent to that of sumatriptan (100 mg p.o.) in a randomized, placebo-controlled clinical trial in 668 patients. Both active drugs were superior to placebo, and the doses of almotriptan were not significantly different from the sumatriptan dose (14) (Box 3).

Data from the first randomized, placebo-controlled study of subcutaneous almotriptan was presented in 1997 and was based on 123 migraine inpatients who received 2, 6 or 10 mg of almotriptan or placebo. Almotriptan 6 mg and 10 mg elicited response rates of >90%, compared to 61.2% for almotriptan 2 mg and 50% for placebo. In addition, pain after 1 h, use of escape medication, duration of attack, nausea, vomiting, phonophobia and photophobia improved more with the two higher doses of the drug. Transient irritation at the site of injection was reported by many patients, but was not dose-related. No serious adverse events occurred (15) (Box 4).

Almotriptan was very well tolerated. In clinical trials, the incidence of adverse events after single doses of 6.25 and 12.5 mg was 13 and 18%, respectively, compared to 16% for placebo. In several phase I trials in healthy volunteers, the incidence of adverse events was low after single oral doses of up to 50 mg. In a group of 24 healthy volunteers and in patients with migraine, almotriptan (12.5, 25 or 50 mg) did not induce clinically significant ECG abnormalities. No differences were observed in mean PR, QRS or QTc interval readings or QTc dispersion. No clinically relevant changes were found in BP or heart rate (16, 17).

Conclusions

Almotriptan has a rapid onset of action and provides significant efficacy in terms of pain relief at 30 min and

Box 4: Efficacy of subcutaneous almotriptan in patients with migraine (15).

Design	Randomized, placebo-controlled clinical trial
Population	Inpatients with migraine (n = 123)
Treatments	Almotriptan (A), 2, 6 or 10 mg s.c. Placebo (P)
Results	Response rate: A10 (90.3%) = A6 (96.5%) > A2 (61.2%) ≥ P (50%)

freedom from pain at 1 h. The response rate for pain relief at 2 h is 60-80%, which is equivalent to the highest rate reported for other antimigraine drugs. Almotriptan has a very low recurrence rate and is consistently effective in different patient populations and across attacks. Almotriptan is at least as effective as sumatriptan, the current standard in migraine management, and other antimigraine drugs. Furthermore, it is very well tolerated, with an incidence of adverse events at therapeutic doses similar to that observed after placebo. In clinical trials, the incidence of chest pain has been very low (0.4%), and the incidence of other adverse events and withdrawals due to adverse events has been similar to placebo.

Almotriptan is currently in phase III clinical trials.

Manufacturer

Almirall Prodesfarma S.A. (ES); licensed to Pharmacia & Upjohn Co. (US).

References

1. Fernández Forner, M.D., Puig Duran, C., Crespo Crespo, M.I., Moragues Mauri, J. (Laboratorios Almirall SA). *Process for the preparation of indole derivs.* ES 2084560.

2. Fernández Forner, D. *New aniline derivatives as key intermediates in the synthesis of 5-HT$_{1B/1D}$ receptor agonists.* Res Disclosure 1998, 412: 1088.

3. Pujol Noguera, F., Crespo Crespo, M.I., Puig Durán, C., Fernández Forner, D., Moragues Mauri, J. (Laboratorios Almirall SA). *New indole derivs.* ES 2056025.

4. Fernandez Forner, D., Puig Duran, C., Prieto Soto, J., Noverola, A., Moragues Mauri, J. (Laboratorios Almirall SA). *Indol derivs. for the treatment of migraine.* EP 605697, JP 94511261, US 5565447, WO 9402460.

5. Johnson, K.W., Phebus, L.A., Cohen, M.L. *Serotonin in migraine: Theories, animal models and emerging therapies.* Prog Drug Res 1998, 51: 219-244.

6. Bou, J., Doménech, T., Gras, J., Beleta, J., Llenas, J., Fernández, A.G., Palacios, J.M. *Pharmacological profile of almotriptan, a novel antimigraine agent.* Cephalalgia 1997, 17: 421-422.

7. Bou, J., Cardelus, I., Llenas, J., Fernandez, A.G., Palacios, J.M. *Antimigraine potential of almotriptan in animal models.* Methods Find Exp Clin Pharmacol 1997; 19 (Suppl. A): Abst PA-21.

8. Garcia, E. et al. *A clinical trial to determine the lack of food interaction on the bioavailability of almotriptan, a new 5-HT1B/1D agonist, in healthy volunteers.* 40th Annu Sci Meet Amer Assoc Study Headache (June 26-28, San Francisco) 1998, Abst 22.

9. Cabarrocas, X., Salva, M. *Pharmacokinetic and metabolic data on almotriptan, a new antimigraine drug.* Cephalalgia 1997, 17: 421.

10. Salva, M., Palacios, J.M., Martinez-Tobed, A. *Metabolism of the novel anti-migraine compound almotriptan (LAS 31416) in humans.* 6th Eur ISSX Meet (June 30-July 3, Gothenburg) 1997, Abst 174.

11. Robert, M., Cabarrocas, X. et al. *Efficacy and tolerability of oral almotriptan in the treatment of migraine. Cephalalgia 1998, 18: A406.*

12. Cabarrocas, X., Zayas, J.M. *Efficacy data on oral almotriptan, a novel 5-HT$_{1B/1D}$ agonist.* 40th Annu Sci Meet Amer Assoc Study Headache (June 26-28, San Francisco) 1998, Abst 23.

13. Cabarrocas, X. *Efficacy data on oral almotriptan, a novel 5HT$_{1D}$ agonist.* Cephalalgia 1997, 17: 421.

14. Cabarrocas, X., Zayas, J.M., Suris, M. *Equivalent efficacy of oral almotriptan, a new 5-HT$_{1B/1D}$ agonist, compared with sumatriptan 100 mg.* 40th Annu Sci Meet Amer Assoc Study Headache (June 26-28, San Francisco) 1998, 155.

15. Cabarrocas, X. *First efficacy data on subcutaneous almotriptan, a novel 5-HT$_{1D}$ agonist.* Cephalalgia 1997; 17 (3): 420.

16. Robert, M., Warrington, S. et al. *Electrocardiographic effects and pharmacokinetics of oral almotriptan in healthy subjects.* Cephalalgia 1998, 18: A406.

17. Robert, M., Warrington, S. et al. *Cardiovascular safety of almotriptan in healthy volunteers.* 41st Annu Sci Meet Amer Assoc Study Headache (June 11-13, Boston) 1998, Abst.