HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

15 December 2010

QUTENZA 179 mg, cutaneous patch
B/1 (CIP code: 576 838-4)
B/2 (CIP code: 576 839-0)

Applicant: ASTELLAS PHARMA SAS

Capsaicin
ATC code: N01BX04

List I

Medicinal product reserved for hospital use

Date of Marketing Authorisation (centralised procedure): 15 May 2009

Reason for request: Inclusion on the list of medicines approved for hospital use.

Division for Medical, Economic and Public Health Assessment

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Capsaicin

1.2. Indication

"QUTENZA is indicated for the treatment of peripheral neuropathic pain in non-diabetic adults either alone or in combination with other medicinal products for pain."

1.3. Dosage (see SPC)

"QUTENZA should be applied to the most painful skin areas (using up to a maximum of 4 patches). The painful area should be determined by the physician and marked on the skin. QUTENZA must be applied to intact, non-irritated, dry skin, and allowed to remain in place for 30 minutes for the feet (e.g. HIV-associated neuropathy) and 60 minutes for other locations (e.g. post-herpetic neuralgia). QUTENZA treatments may be repeated every 90 days, as warranted by the persistence or return of pain.

The QUTENZA cutaneous patch should be applied by a physician or by a health care professional under the supervision of a physician.
Nitrile gloves should be worn at all times while handling QUTENZA and cleaning treatment areas. Latex gloves should NOT be worn as they do not provide adequate protection.

Patches should not be held near eyes or mucous membranes.
Direct contact with QUTENZA, used gauze or used cleansing gel should be avoided.
If necessary, hairs in the treatment area should be clipped to promote patch adherence (do not shave). The treatment area(s) should be gently washed with soap and water. Following hair removal and washing, the skin should be thoroughly dried.
The treatment area should be pre-treated with a topical anaesthetic prior to application of QUTENZA to reduce application-related discomfort. The topical anaesthetic should be applied to cover the entire QUTENZA treatment area and surrounding 1 to 2 cm. The topical anaesthetic should be used in accordance with the product's instructions for use. In clinical trials, patients were pre-treated with a 4% topical lidocaine for 60 minutes.
QUTENZA is a single-use patch and can be cut to match the size and shape of the treatment area. QUTENZA should be cut prior to removal of the release liner. The release liner should NOT be removed until just prior to application. There is a diagonal cut in the release liner to aid in its removal. A section of the release liner should be peeled and folded and the adhesive side of the printed patch placed on the treatment area. The patch should be held in place. The release liner should slowly and carefully be peeled from underneath with one hand while the patch should simultaneously be smoothed onto the skin with the other.

To ensure QUTENZA maintains contact with the treatment area, stretchable socks or rolled gauze may be used.
The QUTENZA patches should be removed gently and slowly by rolling them inward to minimise the risk of aerosolisation of capsaicin. After removal of QUTENZA, cleansing gel should be applied liberally to the treated area and left on for at least one minute. Cleansing gel should be wiped off with dry gauze to remove any remaining capsaicin from the skin. After the cleansing gel has been wiped off, the treated area should be gently washed with soap and water.
Acute pain during and following the procedure should be treated with local cooling (such as a cool compress) and oral analgesics (e.g. short-acting opioids).

Patients with renal and/or hepatic impairment
No dose adjustment is required for patients with renal or hepatic impairment.

Paediatric population
QUTENZA is not recommended for use in children and adolescents due to lack of data on safety and efficacy."

1.4. Special warnings and precautions for use (see SPC)

"Exposure of the skin to capsaicin results in transient erythema and burning sensation.

As a result of treatment-related increases in pain, transient increases in blood pressure (on average <8.0 mmHg) may occur during and shortly after the QUTENZA treatment. Blood pressure should be monitored during the treatment procedure. Patients experiencing increased pain should be provided with supportive treatment such as local cooling or oral analgesics (i.e. short-acting opioids). For patients with unstable or poorly controlled hypertension or a recent history of cardiovascular events, the risk of adverse cardiovascular reactions due to the potential stress of the procedure should be considered prior to initiating QUTENZA treatment.

Patients using high doses of opioids may not respond to oral opioid analgesics when used for acute pain during and following the treatment procedure. A thorough history of the patient should be reviewed prior to initiating treatment and an alternative pain-reduction strategy should be put in place prior to QUTENZA treatment in patients with suspected high opioid tolerance."

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2010)

N: Nervous system
N01: Anaesthetics
N01B: Local anaesthetics
N01BX: Other local anaesthetics
N01BX04: Capsaicin

2.2. Medicines in the same therapeutic category

None

2.3. Medicines with a similar therapeutic aim

- Proprietary medicinal products indicated in the treatment of peripheral neuropathic pain in adults:

Tricyclic antidepressants:
- Amitriptyline: LAROXYL
- Clomipramine: ANAFRANIL
- Imipramine: TOFRANIL

Antiepileptics:
- Gabapentin: NEURONTIN
- Pregabalin: LYRICA
- Carbamazepine: TEGRETOL[1]

- Proprietary medicinal products indicated only in the treatment of postherpetic neuralgia:

Local anaesthetic (patch):
- Lidocaine: VERSATIS 5%

- Proprietary medicinal products indicated in the treatment of intractable pain in adults, including opioids.

[1] Carbamazepine is not recommended, as its efficacy was only suggested by historical studies.

3. ANALYSIS OF AVAILABLE DATA

In support of its application, the company has submitted 12 phase II and III studies:
- 4 non-comparative studies (C106, C109, C111 and C118)
- 8 randomised, double-blind, comparative studies conducted to assess the efficacy and safety of a QUTENZA patch (8% capsaicin), alone or in combination with standard management (antidepressants, antiepileptics, opioids in 50% to 80% of patients, depending on the study), compared with an 0.04% capsaicin patch, which included:
    - 5 studies in postherpetic neuralgia:
        - 2 phase III pivotal studies (C116 and C117)
        - 2 phase III supportive studies (C108 and C110)
        - 1 phase II study which only included 28 patients (C102)
    - 3 studies in HIV-related neuropathic pain:
        - 2 phase III pivotal studies (C107 and C119)
        - 1 phase III supportive study, which was discontinued because of problems in study execution (C112).

3.1. Efficacy results of the comparative studies

In three out of the six controlled, randomised double-blind studies (tabled and summarized in annex) comparing 8% capsaicin with low-dose (0.04%) capsaicin similar to a placebo, the statistically significant difference observed in the absolute value for the primary endpoint "change in mean pain score", evaluated according to the NPRS scale, was weak (of the order of -1.5 to -1.7 relative to baseline, depending on the study) and not clinically relevant[2]. This was observed in two pivotal studies in postherpetic neuralgia and in one pivotal study in HIV-related neuropathic pain.
This difference was not statistically significant in the two supportive studies in postherpetic neuralgia and in one study in HIV-related neuropathic pain.
The effect of very low-dose capsaicin was non-negligible (of the order of 1.2 on the NPRS scale), rendering the difference between the groups of little clinical relevance.

In light of the results of these studies (significant results in some studies, but not in others in which the same treatment models were evaluated), the EMA asked the company to carry out a post-hoc analysis of the results of all the studies. Based on the results of this analysis, combining the results at 60 min for postherpetic neuralgia and at 30 min for HIV-related neuropathic pain, the Marketing Authorisation was granted[3].

[2] Numerical pain evaluation scale from 0 (absence of pain) to 10 (worst pain imaginable). A change of at least 2 points on the NPRS scale relative to baseline is considered clinically relevant. Farrar JT et al. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain 2001 Nov; 94(2): 149-58
cf. CHMP Assessment report for QUTENZA. EPAR p. 35
[3] cf CHMP Assessment report for QUTENZA. EPAR p. 29

3.2. Adverse effects (see SPC)

"Of the 1327 patients treated with QUTENZA in randomised controlled trials, 883 (67%) reported adverse reactions considered related to the medicinal product by the investigator.
The most commonly reported adverse reactions were transient application site burning, pain, erythema and pruritus.
Adverse reactions were transient, self-limited and usually mild to moderate in intensity.
In all controlled studies, the discontinuation rate due to adverse reactions was 0.8% for patients receiving QUTENZA and 0.6% for patients receiving the control.

The adverse effects reported most frequently were as follows:
- Very common (frequency ≥ 1/10): application site pain, application site erythema
- Common (frequency ≥1/100 and <1/10): application site pruritus, application site papules, application site vesicles, application site oedema, application site swelling, application site dryness.

No treatment-related reductions in neurological function, as assessed by Quantitative Sensory Testing (QST) and neurological examinations, have been observed during clinical studies in patients with peripheral neuropathic pain. Temporary, minor changes in heat detection (1℃ to 2℃) and sensitivity to sharp obj ects were detected at the QUTENZA application site in healthy volunteer studies."

3.3. Conclusion

Efficacy in postherpetic neuralgia appears to be real although limited. It seemed less evident in HIV-related neuropathic pain, one study (study C119) having shown an absence of efficacy, possibly due to the very high variability in physiopathology. The authors of a meta-analysis[4] consider that additional studies are necessary to evaluate this product.

A study versus standard management (with antidepressants or antiepileptics) would have permitted determination of the contribution of QUTENZA to the management of peripheral neuropathic pain.

[4] Derry S. et al. Topical capsaicin for chronic neuropathic pain in adults. Cochrane Database of Systematic Reviews 2009, Issue 4.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Neuropathic pain is a chronic condition. It can occur in numerous clinical situations, for example in diabetic neuropathy, secondary to shingles, herpes, HIV or stroke, after an amputation (phantom limb pain), or following surgery or trauma.
Neuropathic pain can be spontaneous, combining the occurrence of both breakthrough pain (like an electric shock) and persistent, underlying pain (burning sensations). It can also be provoked. Sensory disorders may occur concomitantly. Such pain can have significant repercussions (fatigue, anxiety, depression) that impair quality of life.

The proprietary medicinal product QUTENZA is intended for the symptomatic treatment of (non-diabetic) peripheral neuropathic pain.

Efficacy/adverse effects ratio:
In light of the data available, the efficacy/safety ratio of QUTENZA is modest in non-diabetic peripheral neuropathic pain.
The degree of the effect and the long-term maintenance of efficacy have yet to be clarified.

Therapeutic use[5,6,7,8,9,10,11] :

Management of peripheral neuropathic pain
Neuropathic pain responds poorly, if at all, to standard analgesic treatments (NSAIDs, paracetamol). Other therapeutic categories need to be considered. The scientific data available on these therapeutic categories mainly concern the chronic neuropathic pain of diabetic polyneuropathies and postherpetic neuralgia
Treatments for neuropathic pain have moderate efficacy, this being a reflection not only of the placebo effect but also of the difficulty in identifying factors predictive of the response to treatment based on existing studies. Their efficacy seems broadly similar for most aetiologies, though there are exceptions, such as chronic radiculopathies and HIV neuropathies which seem more refractory to existing therapies.
Drug therapies for neuropathies are, by consensus (grade A), based on the use of tricyclic antidepressants (amitriptyline, imipramine, clomipramine) or of antiepileptics (gabapentin or pregabalin), whose safety profile may limit their prescription.
The efficacy of strong opioids (oral morphine) and tramadol[12] is established in peripheral neuropathic pain, particularly in diabetic neuropathy and post-herpetic neuropathy. The prescription of strong opiates is recommended for the treatment of chronic neuropathic pain of persistent high intensity after failure of first-line treatments used as monotherapy, and where appropriate in combination (professional consensus). Prescription in such cases must be subject to all the usual precautions for long-term opiate use.

[5] V. Martinez, N. Attal, D. Bouhassire, M. Lantéri-Minet, for the French Society for the Study and Treatment of Pain. Les douleurs neuropathiques chroniques : diagnostic, évaluation et traitement en médecin ambulatoire. Recommandations pour la pratique clinique de la Société française d'étude et de traitement de la douleur.. Douleurs. Volume 11, p. 3-21. February 2010
[6] V. Martinez, M. Lantéri-Minet. Traitements pharmacologiques actuels, recommandations et perspectives des douleurs neuropathiques. Douleur analg. (2010) 23: 93-98
[7] Eisenberg E et al. Efficacy and safety of opiod agonists in the treatment of neuropathic pain of nonmalignant origin: systematic review and meta-analysis of randomized controlled trials. JAMA. 2005;293(24):3043-52.
[8] Maizels et al. Antidepressants and antiepileptic drugs for chronic non-cancer pain. Aafp 2005 : 71 (3): 483-490
[9] Saarto T, Wiffen PJ.Antidepressants for neuropathic pain. The Cochrane Collaboration. 2005.
[10] Wiffen P et al. Anticonvulsant drugs for acute and chronic pain. The Cochrane Collaboration. 2005
[11] N. Attal et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. European Journal of Neurology 2010, 17 : 1113-1123
[12] Tramadol is recommended as first-line therapy when a strong nociceptive component is associated with neuropathic pain.

According to expert recommendations[13,14,15], lidocaine patches are the first-line treatment when lesions are localised, particularly in elderly patients with allodynia and individuals in whom systemic treatment is contraindicated or inadvisable.

Since the efficacy of treatments is often only partial, combinations of analgesics with complementary mechanisms of action can be proposed.
Optimum therapeutic management of the patient requires regular assessment and adjustments to the treatment strategy as the underlying disease evolves.
The treatment of chronic pain often requires the inclusion of non-medicinal management based on the use of physical and/or psychotherapeutic treatments.

Therapeutic use of QUTENZA:
According to the recommendations of the French Society for the Study and Treatment of Pain[4], the usefulness of this treatment derives from the low risk of systemic adverse effects and the prolonged duration of the effect, subject to the availability of long-term data. However, the initial application is often painful, causing burning sensations and necessitating monitoring of the patient. Application of the capsaicin patch requires compliance with an exact and specific procedure. The very long-term effects of repeated applications on perception of capsaicin are as yet unknown. The data currently available are limited.
In HIV-related neuropathic pain, its role is difficult to establish given the limited study data available. In the course of HIV infection, a great variety of peripheral neuropathies may be observed at all stages of HIV infection (opportunistic infection, polyradiculoneuritis, multiple neuritis, etc.).
Distal sensory polyneuropathy (DSPN) is the most common. In the absence of a specific physiopathological mechanism, aetiological treatment is not an option. Virological success and immune restoration do not always enable a marked clinical improvement. The potentially incriminated medicinal product should be withdrawn, which generally enables an improvement in symptoms. The treatment of DSPN is based on standard combinations of anticonvulsants (gabapentin, pregabalin, lamotrigine), antidepressants and opiate analgesics. In the most intractable cases, management by a centre for the evaluation and treatment of pain is recommended[16].

The proprietary medicinal product QUTENZA should be restricted to patients who have failed to respond to standard therapies for non-diabetic neuropathic pain and are treated in centres specialised in pain management, considering the procedure for its application.
Alternative drug therapies are few in number and of moderate efficacy (therapeutic need not currently met).

Public health benefit:
In view of its frequency and psychosocial consequences (fatigue, anxiety, depression) and the impact of chronic pain on quality of life and everyday activities, the public health burden represented by non-diabetic peripheral neuropathic pain can be regarded as moderate.
Improving the management of pain constitutes a public health need which forms part of established priorities (French Law of 9 August 2004 concerning public health policy, plan for the improvement of pain management 2006-2010).

[13] Lang P-O et al. Zona des sujets âgés. Presse Med 2009; 38: 571-583.
[14] V. Martinez, N. Attal, D. Bouhassire, M. Lantéri-Minet, Les douleurs neuropathiques chroniques : diagnostic, évaluation et traitement en médecin ambulatoire. Recommandations pour la pratique clinique de la Société française d'étude et de traitement de la douleur. Douleur analg . 2010; 11:3-21.
[15] V. Martinez, M. Lantéri-Minet. Traitements pharmacologiques actuels, recommandations et perspectives des douleurs neuropathiques. Douleur analg. 2010; 23: 93-98
[16] Yéni P. Prise en charge des personnes infectées par le VIH. Ecommandations du groupe d'experts (www.sante.gouv.fr). 2010 Report, preliminary version (Special edition "AIDS 2010" (Vienna, 18-23 July 2010)").

In light of the available data (limited analgesic effect) and in the absence of comparative data versus the therapeutic alternatives available, it is difficult to presume an effect for QUTENZA on morbidity (including quality of life).
Moreover, given the strict conditions for its application, necessitating the clinical monitoring of the patient, preferably in a day hospital, during application and the use of analgesics, the proprietary medicinal product QUTENZA can be expected to increase the use of health system resources.
The proprietary medicinal product QUTENZA should not therefore make an additional contribution towards meeting an identified public health need.
Consequently, in the current state of knowledge and because other treatments are currently available, the proprietary medicinal product QUTENZA is not expected to benefit public health.

Conclusion:
In the light of all this evidence, the Committee considers that the actual benefit of QUTENZA is moderate.

4.2 Improvement in actual benefit

QUTENZA provides no improvement in actual benefit (IAB (V) for the management of non-diabetic neuropathic pain in patients who do not respond to treatments that are already available and recommended.

4.3. Therapeutic use

See section 4.1.

4.4. Target population

According to the Guide to the Correct Use of LYRICA, issued by the HAS in 2007, the number of patients in France affected by peripheral neuropathic pain is estimated at between 250,000 and 450,000.
About 25% of these patients[17] suffer from neuropathic pain of diabetic origin. This population does not fall within the scope of treatment with QUTENZA.
According to the results of an epidemiological study[18], 79% of patients are treated with either antiepileptics, antidepressants or opioids and 41% of these patients experienced relief to only a limited extent by these treatments and could benefit from treatment with QUTENZA.
The target population for QUTENZA can thus be estimated at between 60,000 and 110,000 patients. This population is a maximum estimate. In reality, this figure is likely to be smaller, as the administration of QUTENZA must be restricted to pain management centres trained in handling this product.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines approved for hospital use and various public services.

The Transparency Committee has requested:
- a reassessment of this product in 2 years' time, notably in the context of updated clinical data,
- a restriction on the use of QUTENZA by centres specialised in pain management.

[17] Anne M. McDermott et al. The burden of neuropathic pain: results from a cross-sectional survey. European Journal of Pain 10 (2006) 127- 135

Request for a post-registration study:
In view of:

- the strict conditions for the application of this product, necessitating a day hospitalisation with medical surveillance of the patient and precautions to be taken when applying and removing the patch (gloves, cleaning),
- the limited data available regarding repeated use of the product,
- the insufficient data available on evolutions in concomitant prescriptions of analgesics,

the Transparency Committee requests that the company should supply additional data on the conditions of use of QUTENZA in everyday practice.

The Transparency Committee thus asks the company to supply data that will enable:
- a description of the characteristics of the population receiving QUTENZA (clinical situations, previous treatments, etc.);
- a description of the conditions of patients management (speciality and site of practice of the prescribing physician, places where supplied, sites and methods for application of the patch);
- an assessment of the long-term effects of repeated applications of capsaicin in terms of impact on pain perception and quality of life;
- determination of its impact on the consumption of drug therapies for neuropathic pain (tricyclic antidepressants, antiepileptics, opioids, etc.).

ANNEX

1) Studies in postherpetic neuralgia

Methodology	Studies	Objective	Primary efficacy endpoint	Results for the primary efficacy endpoint				
Randomised double-blind, controlled pivotal studies	**C116** N = 402	Evaluation of the efficacy and safety of the application for 60 min of a QUTENZA 8% patch versus another patch containing 0.04% capsaicin Duration: 12 weeks	Change in mean pain score measured after 8 weeks of treatment (expressed in %) This score was evaluated by the patient every 24 h using the Numerical Pain Rating Scale (NPRS)	**Pain score**	**QUTENZA 8% versus 0.04% patch (n = 206) (n = 196)**			**p value of the difference**
				Mean value at inclusion	6.0 (0.1) vs. 5.8 (0.1)			
				Absolute change after treatment	- 1.7 (0.1) vs. - 1.2 (0.1)			0.0024
				% change	-29.6 (2.0) vs. -19.9 (2.1)			0.0010
	C117 N = 416			**Pain score**	**QUTENZA 8% versus 0.04% patch (n = 212) (n = 204)**			**p value of the difference**
				Mean value at inclusion	5.7 (0.1) vs. 5.8 (0.1)			
				Absolute change after treatment	- 1.7 (0.1) vs. - 1.3 (0.1)			0.0344
				% change	- 32.0 (2.1) vs. -24.4 (2.1)			0.0108
Randomised double-blind, controlled supportive studies	**C108** N = 299	Evaluation of the efficacy and safety of the application for 30, 60 or 90 min of a QUTENZA 8% patch versus another patch containing 0.04% capsaicin Duration: 12 weeks		**Pain score**	**QUTENZA 8% versus 0.04% patch (n = 222) (n = 77)**			
					30 min (n = 72)	60 min (n = 77)	90 min (n = 73)	Patch 0.04% Overall result
				Mean value at inclusion	5.8 (0.2)	5.4 (0.2)	5.6 (0.2)	5.3 (0.2)
				Absolute change after treatment	- 1.4 (0.2)	- 1.3 (0.2)	- 1.4 (0.2)	- 1.0 (0.2)
				% change	- 27.7 (3.6)	- 25.6 (3.6)	- 27.8 (3.7)	- 17.3 (3.6)
				p value of the difference	**NS**	**NS**	0.0438	
	C110 N = 155	Evaluation of the efficacy and safety of the application for 60 min of a QUTENZA 8% patch versus another patch containing 0.04% capsaicin Duration: 12 weeks		**Pain score**	**QUTENZA 8% versus 0.04% patch (n = 102) (n = 53)**			**p value of the difference**
				Mean value at inclusion	5.4 (0.2) vs. 5.3 (0.2)			
				Absolute change after treatment	- 1.8 (0.2) vs. - 1.6 (0.3)			**NS**
				% change	- 36.5 (3.7) vs. -29.9 (5.1)			**NS**

2) Studies in HIV-related neuropathic pain

<table>
<tr><th>Methodology</th><th>Studies</th><th>Objective</th><th>Primary efficacy endpoint</th><th colspan="6">Results for the primary efficacy endpoint</th></tr>
<tr><td rowspan="11">Randomised double-blind, controlled pivotal studies</td><td rowspan="5">C107
N = 307</td><td rowspan="5">Evaluation of the efficacy and safety of the application for 30, 60 or 90 min of a QUTENZA 8% patch versus another patch containing 0.04% capsaicin

Duration: 12 weeks</td><td rowspan="11">Change in mean pain score measured after 12 weeks of treatment (expressed in %)

This score was evaluated by the patient every 24 h using the Numerical Pain Rating Scale (NPRS)</td><td rowspan="2">Pain score</td><td colspan="5">QUTENZA 8% versus 0.04% patch
(n = 225) (n = 82)</td></tr>
<tr><td>30 min
(n = 72)</td><td>60 min
(n = 78)</td><td>90 min
(n = 75)</td><td colspan="2">Patch 0.04%
Overall result</td></tr>
<tr><td>Mean value at inclusion</td><td>5.9 (0.2)</td><td>5.8 (0.2)</td><td>6.1 (0.2)</td><td colspan="2">5.9 (0.2)</td></tr>
<tr><td>Absolute change after treatment</td><td>- 1.5 (0.2)</td><td>- 0.9 (0.2)</td><td>- 1.3 (0.2)</td><td colspan="2">- 0.6 (0.2)</td></tr>
<tr><td>% change</td><td>- 27.7 (3.6)</td><td>- 15.8 (3.4)</td><td>- 24.7 (3.5)</td><td colspan="2">- 10.7 (3.4)</td></tr>
<tr><td>p value of the difference</td><td>0.0007</td><td>NS</td><td>0.0046</td><td colspan="2"></td></tr>
<tr><td rowspan="6">C119
N = 484</td><td rowspan="6">Evaluation of the efficacy and tolerance of the application for 30 or 60 min of a QUTENZA 8% patch versus another patch containing 0.04% capsaicin

Duration: 12 weeks</td><td rowspan="2">Pain score</td><td colspan="3">QUTENZA 8% (n = 322)</td><td colspan="2">0.04% Patch (n = 162)</td></tr>
<tr><td>30 min
(n = 167)</td><td>60 min
(n = 165)</td><td>30 min
(n = 73)</td><td>60 min
(n = 89)</td></tr>
<tr><td>Mean value at inclusion</td><td>6.0 (0.1)</td><td>6.2 (0.1)</td><td>5.9 (0.2)</td><td>5.9 (0.2)</td></tr>
<tr><td>Absolute change after treatment</td><td>- 1.6 (0.0)</td><td>- 2.0 (0.1)</td><td>- 1.1 (0.2)</td><td>- 1.8 (0.2)</td></tr>
<tr><td>% change</td><td>- 26.1 (2.4)</td><td>- 32.8 (2.4)</td><td>- 19.1 (3.6)</td><td>- 30.1 (3.3)</td></tr>
<tr><td>p value of the difference</td><td>NS</td><td>NS</td><td></td><td></td></tr>
</table>

During all studies, 50% to 80% of patients received concomitant treatments (opioids, anticonvulsants, antidepressants).