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TRANSPARENCY COMMITTEE
Opinion
17 September 2014

ALTIM 3.75 mg/1.5 ml, suspension for injection

1 1.5 ml pre-filled syringe (CIP: 34009 313 579 8 8)

Applicant: SANOFI-AVENTIS France

INN	Cortivazol
ATC Code (2013)	H02AB17 (glucocorticoids)
Reason for the review	Re-assessment of the Actual Benefit of medicinal products indicated in radiculalgia by epidural injection at the Committee’s request, in compliance with article R-163-21 of the French Social Security Code
List concerned	National Health Insurance (French Social Security Code L.162-17) Hospital use (French Public Health Code L.5123-2)
Indication concerned	“In epidural injection: radiculalgia”

Actual Benefit	Low
Therapeutic use	This proprietary medicinal product is a second-line treatment, in patients who have been properly informed of the risks inherent in this practice, in certain forms of radiculalgia that have been present for several months and which are resistant to well-conducted medical treatments.

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	Date of Marketing Authorisation (national procedure): 30/12/1997
Prescribing and dispensing conditions /special status	List I
ATC Classification	2013 H Systemic hormones, sex hormones excluded H02 Corticosteroids for systemic use H02A Corticosteroids for systemic use, plain H02AB Glucocorticoids H02AB17 Cortivazol

02 BACKGROUND

On 26 November 2008, as part of the renewal of its inclusion, the Transparency Committee concluded that the actual benefit of ALTIM (cortivazol) was substantial in the indications of the Marketing Authorisation.

On 20 November 2013, the Transparency Committee concluded that the actual benefit of HYDROCORTANCYL 2.5% suspension for injection (prednisolone), the only clinically relevant comparator, was substantial in all the indications of the Marketing Authorisation except radiculalgia, where it was still insufficient.

On 5 February 2014, during the examination of the renewal of the inclusion of ALTIM, the Transparency Committee wished to defer its opinion in the indication “treatment of radiculalgia by epidural injection” while awaiting the joint re-assessment of HYDROCORTANCYL and ALTIM, the only corticosteroids with this indication in France.

The objective of this re-assessment of the proprietary medicinal products HYDROCORTANCYL (prednisolone) and ALTIM (cortivazol) in their use as epidural injections is, in particular, to take stock of the available clinical data and to define their place in the treatment strategy for radiculalgia.

03 THERAPEUTIC INDICATIONS

“They are those of topical corticosteroids when the disease justifies a high local concentration. Any local injection prescription should take the danger of infection into consideration, in particular the risk of bacterial growth being promoted.

This product is indicated in rheumatological diseases:

- In intra-articular injection: inflammatory arthritis, advanced osteoarthritis.
- In periarticular injection: tendinitis, bursitis.
- In injection of soft tissue: talalgia, carpal tunnel syndrome, Dupuytren’s contracture.
- In epidural injection: radiculalgia.”

04 DOSAGE

Equivalent antiinflammatory (equal potency) doses for 5 mg prednisone = 0.3 mg cortivazol.

Do not administer intravenously or intramuscularly.

The dose usually used is 0.5 to 1.5 ml depending on the location - whether intra-articular, periarticular, or epidural injection and whether a single or repeated dose (usually at intervals of 1 to 3 weeks).

NB: Do not use more than 1.5 ml per session no matter how many joints are injected.

05 THERAPEUTIC NEED

Lumbar radiculalgia originating from the discs, a common condition, corresponds to compression by a herniated disc of the L3 or L4 (cruralgia) or L5 or S1 (sciatica) nerve roots, resulting in back pain with radicular radiation into the lower limbs, sometimes together with or replaced by distal paresthesia.

Irrespective of the fate of the herniated disc, changes in the direction of recovery/regression can occur spontaneously, generally after a few months: 80% at 2 months, 95% at 1 year. L5 or S1 paralysis or, very rarely, by cauda equina syndrome can occur as complications of lumbosciatica. Later relapses are possible, as is persistence of back pain after the acute episode.

The annual prevalence of common lumbosciatica is about 2% in the adult population, with a peak frequency between 40 and 60 years of age. The principle predisposing factors are excessive mechanical stress on the back, especially when accompanied by repeated flexion-extension or torsional movements of the trunk.

Cervicobrachial neuralgia results from damage to a nerve root in the brachial plexus (5th, 6th, 7th, 8th cervical or 1st thoracic). It falls into two categories, common cervicobrachial neuralgia and symptomatic cervicobrachial neuralgia (inflammatory, infectious, neoplastic). Among the common cervicobrachial neuralgias, neuralgias of arthritic origin, especially after the age of 40, are due to compression by a protruding disc or bone spur; cervicobrachial neuralgias originating from the discs, especially among younger subjects, result from compression by a "soft hernia".

The objectives of the treatment of radiculalgia are:

- Treatment of pain,
- The identification of patients who require urgent surgical intervention,
- The prevention of recurrence

The first line treatment of radiculalgia comprises rest, NSAIDs for a short period and analgesics. Muscle relaxants are sometimes used.

The administration of corticosteroids by epidural injection for the treatment of intractable lumbar radiculalgia and cervicobrachial neuralgia, the usual causes of which are herniated discs and spondyloarthropathy, should only be considered after first line treatment has failed (see section 011: Therapeutic use).

Non-medicinal treatments include spinal traction, back braces or corsets. Surgery is a last resort treatment.

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

Name (INN) Company	Same TC* Yes / No	Indications	Date of Opinion	AB	Reim- bursed Yes/No
HYDROCORTANCYL 2.5 percent, suspension for injection (Prednisolone) Sanofi-Aventis France	Yes	<p>They are those of topical corticosteroids when the disease justifies a high local concentration. Any local injection prescription should take the danger of infection into consideration, in particular the risk of bacterial growth being promoted.</p> <p>This medicinal product is indicated in the following diseases:</p> <ul style="list-style-type: none"> <input type="checkbox"/> Rheumatological: <ul style="list-style-type: none"> o intra-articular injections: inflammatory arthritis, advanced osteoarthritis, o periarticular injections: tendinitis, bursitis, o injections into soft tissue: talalgia, carpal tunnel syndrome, Dupuytren's contracture. o epidural injections: radiculalgia, o intradural injections: radiculalgia in the event of failure of other treatments (resistant to epidural injections) or when analysing cerebrospinal fluid. <input type="checkbox"/> Dermatological: <ul style="list-style-type: none"> keloid scars. <input type="checkbox"/> Neoplastic: <ul style="list-style-type: none"> intradural injections in leukaemic and neoplastic meningitis. <input type="checkbox"/> Ophthalmological: <ul style="list-style-type: none"> periocular injections in certain inflammatory conditions of the anterior segment with involvement of the intermediate uvea. <input type="checkbox"/> ENT: <ul style="list-style-type: none"> intra-sinus irrigation in subacute or chronic sinusitis requiring drainage. 	20 November 2013	The actual benefit remains substantial in the indication of the Marketing Authorisation apart from radiculalgia, where it remains insufficient.	Yes

Some NSAIDs are indicated in the short-term treatment of radiculalgia, with administration by the oral (alminoprofen, diclofenac, etodolac, flurbiprofen, ibuprofen, indomethacin, ketoprofen, naproxen and tenoxicam) or rectal (indomethacin, ketoprofen and naproxen) route or by intramuscular injection (ketoprofen).

Analgesics and muscle relaxants are also alternatives in this indication.

06.2 Other health technologies

Spinal traction, back braces or corsets may be indicated in radiculalgia. Surgical treatment remains a last resort.

► Conclusion

This is a single clinically relevant comparator that is indicated in the treatment of radiculalgia by epidural injection: **HYDROCORTANCYL 2.5% suspension for injection (prednisolone)**.

07 SUMMARY OF PREVIOUS ASSESSMENTS

ALTIM 3.75 mg/1.5 ml, suspension for injection in a prefilled syringe			
Indications	<p>They are those of topical corticosteroids when the disease justifies a high local concentration.</p> <p>Any local injection prescription should take the danger of infection into consideration, in particular the risk of bacterial growth being promoted.</p> <p>This product is indicated in rheumatological diseases:</p> <ul style="list-style-type: none"> - In intra-articular injection: inflammatory arthritis, advanced osteoarthritis. - In periarticular injection: tendinitis, bursitis. - In injection of soft tissue: talalgia, carpal tunnel syndrome, Dupuytren's contracture. - In epidural injection: radiculalgia 		
Date of Opinion (reason for the review)	19 November 1999 (Actual benefit)	26 November 2008 (Renewal of inclusion)	5 February 2014 (Renewal of inclusion)
Actual Benefit	<p>Level of actual benefit for this proprietary medicinal product: substantial</p> <p>The epidural injections had marginal use and they do not provide any actual benefit.</p>	<p>The actual benefit of these proprietary medicinal products remains substantial in the Marketing Authorisation indications.</p>	<p>The Committee considers that the actual benefit of ALTIM remains substantial in rheumatological diseases:</p> <ul style="list-style-type: none"> - In intra-articular injection: inflammatory arthritis, advanced osteoarthritis. - In periarticular injection: tendinitis, bursitis. - In injection of soft tissue: talalgia, carpal tunnel syndrome, Dupuytren's contracture. <p>The Committee does not make any comment on the actual benefit of ALTIM in the epidural injection indication: radiculalgia, pending the re-assessment of ALTIM 3.75 mg/1.5 ml suspension for injection and HYDROCORTANCYL 2.5% suspension for injection in this single indication.</p>

08 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

This proprietary medicinal product is not on the market in France.

09 ANALYSIS OF AVAILABLE DATA

The company's dossier includes 4 publications: one French retrospective study and 3 literature reviews not pertaining specifically to cortivazol.

Alberti et al¹ carried out a single-centre (Bordeaux) retrospective study covering 996 patients who were given an infiltration of a mixture of corticosteroids (prednisolone acetate and cortivazol) and an iodinated contrast agent (iopamidol) under CT control between October 2008 and June 2010, which did not reveal any neurological complications. The observed adverse effects were vasovagal responses (21 patients), allergic reactions (3 patients) and exacerbation of the pain (9 patients). This study cannot be taken into account, as only a poster is available.

The review by Bellini et al,² which included articles published in English up to 2012, listed the systemic effects (particularly metabolic, vascular, cardiopulmonary and endocrine effects) of epidural injections of corticosteroids.

The objective of the review by Andreisek et al³ was to identify the methods used for the epidural injections, the location of the injection, the use of imaging, and the type and dose of corticosteroids. Methylprednisolone was the corticosteroid most often administered (43 out of 91 studies), then triamcinolone (29 out of 91 studies), then dexamethasone (4 out of 91 studies) and cortivazol (2 out of 91 studies). According to this publication, most of the injections were foraminal and interlaminar.

The objective of the study by Cohen et al⁴ was to provide an exhaustive review including action mechanisms, efficacy, risks and cost-effectiveness. The authors conclude that epidural steroid injections have some efficacy in the alleviation of pain and the improvement in mobility in selected patients for a period of at least 6 weeks. The longer term efficacy and the ability to reduce the recourse to surgery are controversial. The transforaminal injection, which seems more effective, is not a first-line treatment, because of the risks.

Supplementary investigations have identified the following:

- Two French studies: One relating to the safety of cortivazol⁵ and the other to its clinically relevant comparator prednisolone⁶ (see section 09.2: Safety).
- Several systematic analyses and meta-analyses have been identified.^{7,8,9,10,11,12,13,14} The majority concluded that there is a short-term analgesic effect but no long-term effect. The

¹ Alberti N et al. Foraminal steroid injections performed under CT control: a retrospective study. Poster CIRSE 2013.

² Bellini M, Barbieri M. Anest Systemic effects of epidural steroid injections. *Anaesthesiology Intensive Therapy*. 2013;45:93-98.

³ Andreisek G et al. Access routes and reported decision criteria for lumbar epidural drug injections: A systematic literature review. *Skelet Radiol* 2013;42:1683-1692.

⁴ Cohen SP et al. Epidural steroids: A comprehensive, evidence-based review. *Reg Anesth Pain Med* 2013;38:175-200.

⁵ Depriester et al. CT-guided transforaminal cervical and lumbar epidural injections. *Diagnostic and Interventional Imaging* 2012, 93: 704-710.

⁶ Wybier et al. Paraplegia complicating selective steroid injections of the lumbar spine. Report of five cases and review of the literature. *Eur Radiol* 2010, 20: 181-189.

⁷ Koes BW et al. Efficacy of epidural steroid injections for low-back pain and sciatica: a systematic review of randomized clinical trials. *Pain* 1995 Dec;63(3):279-88.

⁸ Armon C et al. Assessment: use of epidural steroid injections to treat radicular lumbosacral pain: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2007 Mar 6;68(10):723-9.

⁹ Buenaventura et al. Systematic review of therapeutic lumbar transforaminal epidural steroid injections. *Pain Physician* 2009 Jan-Feb;12(1):233-51.

effect is small and its clinical relevance is debatable. No demonstration of the effect on the consumption of systemic analgesics, the level of recourse to surgery, or the duration of incapacity exists. A meta-analysis of the efficacy¹⁵ (Pinto et al, 2012) that included 23 randomised, controlled studies compared epidural injections of corticosteroids (methylprednisolone, triamcinolone, betamethasone, and prednisolone (only 1 study)) with placebo by the 3 principal approaches (caudal, epidural, foraminal). The “intensity of pain” and “disability” scores were converted to a scale from 0 (no pain or disability) to 100 (worst pain experienced or maximum disability). In the short term (between 2 weeks and 3 months), this meta-analysis (14 studies, 1316 patients) showed a significant effect in favour of steroids, with a mean difference of the score for the intensity of pain in the lower limbs of -6.2 (95% CI [-9.4; -3.0]) and $I^2 = 10\%$. An effect of this size does not reach the threshold of clinical relevance. The meta-analysis (6 studies, 723 patients) did not demonstrate a significant effect on the score for intensity of back pain, with a mean difference of 0.5 (95% CI [-3.9; 4.8]) and $I^2 = 0\%$. A significant effect on mobility in favour of steroids was detected, with a mean difference in the disability score of -3.1 (95% CI [-5; -1.2]) and $I^2 = 0\%$. In the long term (> 12 months), no difference between the steroids evaluated and placebo was demonstrated in relation to pain in the lower limbs, back pain or mobility.

09.1 Efficacy

No clinical efficacy data relating to the use of cortivazol or its clinically relevant comparator prednisolone in the treatment of radiculalgia by epidural injection have been identified.

09.2 Safety

9.2.1 Data from the official drug safety survey

In October 2008, an official drug safety survey was set up following neurological adverse effects in the form of cases of paraplegia/tetraplegia after CT-guided injections by the foraminal (i.e. intra-foraminal) or periradicular approach in rheumatic diseases.^{16,17}

This survey showed:

- an increased risk of spinal cord infarction leading to paraplegia after CT-guided lumbar infiltration in patients with a history of spinal surgery. The highest risk seems to relate to the foraminal approach, but events have also been observed after epidural infiltration or

¹⁰ Benny B et al. The efficacy of lumbosacral transforaminal epidural steroid injections: a comprehensive literature review. *J Back Musculoskelet Rehabil* 2011;24(2):67-76.

¹¹ Benyamin RM et al. The effectiveness of lumbar interlaminar epidural injections in managing chronic low back and lower extremity pain. *Pain Physician* 2012 Jul-Aug;15(4):E363-404.

¹² Benoist M et al. Epidural steroid injections in the management of low-back pain with radiculopathy: an update of their efficacy and safety. *Eur Spine J* 2012 Feb;21(2):204-13.

¹³ Manchikanti L et al. Effectiveness of therapeutic lumbar transforaminal epidural steroid injections in managing lumbar spinal pain. *Pain Physician* 2012 May-Jun;15(3):E199-245.

¹⁴ Quraishi N. Transforaminal injection of corticosteroids for lumbar radiculopathy: systematic review and meta-analysis. *Eur Spine J* 2012 Feb;21(2):214-9.

¹⁵ Pinto et al. Epidural Corticosteroid Injections in the Management of Sciatica: A Systematic Review and Meta-analysis. *Ann Intern Med* 2012, 157: 865-877.

¹⁶ Enquête officielle de pharmacovigilance sur les cas de complications neurologiques graves (paraplégie, tétraplégie, infarctus cérébral) rapportées après infiltrations locales de corticoïdes dans les affections du rachis. Rapport pour la Commission Nationale de Pharmacovigilance [Official drug safety survey of cases of serious neurological complications (paraplegia, tetraplegia, cerebral stroke) reported after local infiltrations of corticosteroids in spinal conditions. Report for the National Pharmacovigilance Committee]. 27/01/2009.

¹⁷ Afssaps. Risque de paraplégie/tétraplégie lié aux injections radioguidées de glucocorticoïdes au rachis lombaire ou cervical. Mise au point. [Risk of paraplegia/tetraplegia due to CT-guided injections of glucocorticoids in the lumbar or cervical spine. An update.] March 2011.

posterior articular injection. A neurological adverse event occurred in a patient with no history of spinal surgery after infiltration by the foraminal approach.

- a potentially fatal risk of stroke and spinal cord infarction after CT-guided infiltration into the cervical spine.

All the neurological adverse events (8 cases in the lumbar spine and 4 cases in the cervical spine) were reported after the injection of HYDROCORTANCYL (prednisolone). In fact, because of the habits of practitioners and possibly also because HYDROCORTANCYL is indicated for both epidural and intradural infiltrations (ALTIM is not indicated for intradural infiltrations), it seems that this product, almost exclusively, has been used for CT-guided spinal injections of cortisones. Even though intradural infiltrations are now no longer indicated or performed, an unplanned intradural injection could still occur in the course of an epidural even if the operator is experienced.¹⁸ Epidural haematoma is a complication of epidural injections that, although rare, can be serious. It is more likely in the presence of a coagulation disorder.

The assumed mechanism of neurological events after interlaminar epidural injections in the cervical spine, rarely practiced in France and not reported in the drug safety survey, seems to follow direct injury to the spinal cord or a toxic effect at a distance from the product injected, without a relationship between the vascular topography and lesions observed by MRI. The lumbar events that occur after foraminal, lumbar or cervical injections are of arterial origin. The hypothesis of an embolus of cortisone derivative in a small artery leading to the spinal cord has been formulated. In the operated spine, the epidural scar tissue is hypervascularised. These vessels may be connected to a radiculomedullary artery. The risk of arterial emboli thus appears higher.

In 2011, AFSSAPS [French Healthcare Product Safety Agency] (now ANSM) [French National Agency for Medicines and Health Products Safety] stated that there were no available data to establish the safety of ALTIM.¹⁶ A review of the literature had identified events of the same type reported with several injectable cortisone derivatives, including a single case with cortivazol.

In July 2010, AFSSAPS, in collaboration with the Société française de rhumatologie [French Society of Rheumatology] and the Société française de radiologie [French society of radiology] circulated a letter to healthcare professionals, and, more particularly, radiologists and rheumatologists, providing the following information:

- A description of the occurrence of cases of paraplegia/tetraplegia after CT-guided intraspinal injections of corticosteroids by the foraminal or periradicular approach in rheumatic disorders,
- A reminder of the good use of injectable glucocorticoids and the need to use them in strict conformity with their Marketing Authorisation, particularly in the case of ALTIM and HYDROCORTANCYL, and the need to take into consideration the possible occurrence of serious neurological complications when treating benign conditions.

Following this drug safety survey, the summaries of product characteristics of the two proprietary medicinal products have been modified. No reassessment of the risk/benefit ratio was requested by ANSM.

Following the AFSSAPS alert that followed neurological adverse events involving HYDROCORTANCYL, ALTIM now seems to be used preferentially by practitioners.^{5,19}

9.2.2 Data from a retrospective study with prednisolone

The retrospective study by Wybier et al⁶ analyses the cases of 5 patients with paraplegia following the injection of prednisolone (HYDROCORTANCYL) by the epidural approach between 2003 and 2008. According to the authors, the higher level in France compared with the literature data could

¹⁸ Valat JP Rozenberg S. Les infiltrations de corticoïde dans les lombosciatiques et les lombalgies communes [Injection of corticosteroids in common lumbosciatica and lumbalgia]. *Revue du Rhumatisme* 2008; 75: 590-595.

¹⁹ Krause D, Drapé JL, Spinal infiltration; have you modified your practice. *Diagnostic and interventional imaging* 2013; 94: 1065-67.

be linked to the use of prednisolone acetate, a substance with a tendency to agglomerate, thus increasing the risk of arterial embolism. In 3 of the 5 cases, an anaesthetic (bupivacaine, ropivacaine) was administered with the corticosteroid and may have been involved in the occurrence of the serious adverse events (AE).

9.2.3 Data from a retrospective study with cortivazol

The retrospective, observational single-centre study by Depriester et al⁵ relates to 1529 patients who had a CT guided foraminal injection of cortivazol by the lumbar (75.6%) or cervical (24.4%) approach in 2010. The adverse events were 35 cases (2.3%) of vasovagal syncope (resolved after raising the legs), 5 cases of allergy (0.2%) (resolved after administration of 200 mg of hydrocortisone hemisuccinate) and 3 cases (0.3%) of increased blood pressure (which occurred in patients with hypertension). According to the authors, pain during the injection, which was very frequent (65% of cases), should not be considered an AE. An increase in the intensity of the radiculalgia in the days following the injection of cortivazol was noted in 37.4% of cases, particularly after cervical injections. No serious neurological complications such as paraplegia, tetraplegia or embolism were observed. Recourse to a 2nd epidural injection 4 to 6 weeks after the first was necessary in 21% of cases. In 19% of cases, patients had undergone surgery on the spinal cord before the epidural injection. According to the authors, the cases of serious complications such as tetraplegia or paraplegia that led to the AFSSAPS alert in March 2011 were probably due to arterial embolisms linked to the injection of particles of a microcrystalline form and of a size that contributed to the formation of macro-aggregates. The authors think that efficacy has been demonstrated at the cervical and lumbar level, with a reduction in pain from the 13th day on average, and an average duration of 15 months for 65 to 70% of patients.

9.2.4 PSUR data

The safety data examined in the course of the renewal of the inclusion of ALTIM cover the period from 01 June 2008 to 31 December 2012 (Opinion of the Transparency Committee of 5 February 2014). Since then, no other PSURs have been submitted to ANSM. A supplementary review based on the company's drug safety data relating to reported cases involving ALTIM that were registered between 1 January 2013 and 20 February 2014 does not reveal any particular signal.

09.3 Other data

9.3.1 Prescription data

The data from the IMS panel as a moving annual total for spring 2014 are shown in the table below.

	ALTIM 3.75 mg/1.5 ml, suspension for injection
Number of prescriptions	976,151
Prescriptions by rheumatologists	80%
Principal reasons for prescription (%)	Osteoarthritis of the knee (18%)

This panel does not permit an analysis of the use of ALTIM in the indication "epidural injection: radiculalgia".

010 SUMMARY AND DISCUSSION

The objective of this reassessment is to take stock of the available clinical data on the use of ALTIM (cortivazol) and its clinically relevant comparator, HYDROCORTANCYL (prednisolone) as epidural injections as well as to assess their status relative to each other and in the strategy for the treatment of radiculalgia.

In relation to efficacy, in 2008, a review of the available efficacy data was carried out within the framework of the official drug safety survey¹⁶ relating to the cases of severe neurological complications reported after local infiltrations of corticosteroids in spinal conditions and stated that: “The available data on the efficacy of local injections of glucocorticoids relate mostly to open studies, mostly with limited numbers of patients, which are heterogeneous in relation to a number of parameters: duration of the symptoms, origin of the condition, volume injected, approach, number of injections, time between infiltrations, and corticosteroid used (prednisolone, methylprednisolone acetate, triamcinolone, betamethasone). As with other intra-articular infiltrations, the expected benefit of the infiltration of corticosteroids into the spinal column is to obtain a locally high concentration of the antiinflammatory, permitting inhibition of the synthesis and release of proinflammatory substances.

The results are contradictory, but some well-conducted studies show a significant short-term reduction in pain (1 to 60 days). The long-term benefit is more limited, and no difference in relation to the recourse to surgery has been demonstrated.”

The new data identified (literature reviews, meta-analyses) confirm this assessment and conclude that the weak analgesic effect and clinical relevance are debatable in the short term and that epidural injection of corticosteroids has not been shown to have a long-term effect. Because ALTIM and HYDROCORTANCYL are only used in France, the publications mainly relate to corticosteroids used in other countries: methylprednisolone, triamcinolone, betamethasone and dexamethasone (which do not have Marketing Authorisation in France for the indication “radiculalgia by epidural injection”). No recent studies or comparative data relating to the efficacy of epidural injection specific to these two substances have been identified. Whatever the proprietary medicinal product, the available data represent a low level of evidence. No data relating to a possible reduction in recourse to the use of systemic analgesics, recourse to surgery, or to the duration of incapacity exists.

In relation to safety, since the alert highlighting the rare but serious neurological events, that is to say paraplegia and tetraplegia, that occurred after the injection of HYDROCORTANCYL, no new signal has been identified. Two main risk factors in the lumbar spine have been identified: operated spine and the foraminal approach. According to the publications by Depriester⁵ et de Wybier,⁵ prednisolone seems to present a higher risk of neurological complications than cortivazol; one of the hypotheses formulated was linked to the sizes of the particles. The use of ALTIM in CT-guided infiltrations now seems to be preferred to that of HYDROCORTANCYL.¹⁹

011 THERAPEUTIC USE

Spinal infiltrations can be targeted at:

- The epidural space (interspinous or interlaminar approach or approach via the sacrococcygeal hiatus)
- The intervertebral foramen (foraminal approach)
- The posterior articular space (posterior intra-articular approach)

No recent French or foreign guidelines have been identified. In 2007, the spinal section of the French Society of Rheumatology noted that for lumbosciatica “epidural infiltrations probably ameliorate pain and improve quality of life without radically changing the medium-term prognosis”.²⁰

In cervicobrachial neuralgia, CT-guided cervical epidural infiltrations by the interlaminar approach are still very rarely used in France because of the risk of a direct injury to the spinal cord. The most

²⁰ Legrand E et al. La sciatique par hernie discale : traitement conservateur ou traitement radical ? [Sciatica caused by disc herniation: conservative or radical treatment?] Revue du Rhumatisme 74 (2007): 927–932.

widespread practice was foraminal infiltration, but because of the serious, sometimes fatal, neurological complications that have occurred (anterior spinal artery syndrome leading to tetraplegia, cerebellar stroke), many centres have stopped using this technique.²¹ It has been suggested that these foraminal infiltrations should be replaced by posterior inter-articular infiltrations.^{22,23} Intra-articular opacification guarantees that the injection takes place into a nonvascular space and low-pressure rupture of the joint capsule should permit passage into the central epidural space. However, the level of evidence relating to efficacy is low.

According to AFSSAPS, the indications for CT-guided cortisone injections into the cervical spine are cervicobrachial neuralgia that has been present for several months and which is resistant to well-conducted medical treatments in patients who have been properly informed of the risks inherent in this practice.¹⁶ These measures are considered an alternative to surgical procedures and are only indicated after individual assessment of the risk/benefit ratio, taking into consideration the fact that efficacy has not been formally demonstrated. The low level of evidence of efficacy and knowledge of the risk of serious adverse events do not allow the Committee to formulate guidelines relating to cervical treatment.

In lumbar radiculalgia, infiltrations are still routinely performed by practitioners. Procedures to minimise the neurological risk were defined by AFSSAPS in 2011:

- Operated lumbar spine: CT-guided injections into the operated surgical spine are not recommended. Where appropriate, the decision must be taken at a multidisciplinary case meeting.
- Unoperated lumbar spine: CT-guided foraminal injections only address cases of common lumbar radiculalgia that are resistant to well-conducted medical treatment (which could include interspinous epidural injections) in patients who have been informed of the risks of neurological adverse events.
- In order to avoid arteries leading to the spinal cord, do not catheterise the foramen.

ALTIM's place in the treatment strategy

ALTIM is a second-line treatment, in patients who have been properly informed of the risks inherent in this practice, in certain forms of radiculalgia that have been present for several months and which are resistant to well-conducted medical treatments.

012 **TRANSPARENCY COMMITTEE CONCLUSIONS**

In view of all the above information, and following the debate and vote, the Committee considers that the conclusions in its previous opinion of 26 November 2008 should be amended:

012.1 **Actual benefit**

- ▶ Radiculalgia is not life-threatening, but, as a result of its incapacitating symptoms and chronic nature, has a substantial impact on quality of life.
- ▶ This proprietary medicinal product is intended as symptomatic therapy.

²¹ Wybier M. Injections cortisonées radioguidées du rachis cervical (ce que je fais, ce que je ne fais plus) [CT-guided cortisone injections in the cervical spine (what I do, what I no longer do)]. *Rev Rhum* 2008; 75: 755-62.

²² Wybier M. Lumbar epidural and foraminal injections: update. *J Radiol* 2010; 91: 1079-85.

²³ Bureau NJ et al. Transforaminal versus Intra-Articular Facet Corticosteroid Injections for the Treatment of Cervical Radiculopathy: A Randomized, Double-Blind, Controlled Study. *AJNR Am J Neuroradiol*. 2014 Aug;35(8):1467-74.

▶ The data, which provide a low level of evidence, suggest a low level of efficacy against pain in the short term. The available safety data do not reveal any new signals. The efficacy/adverse effects ratio for this medicinal product is low.

▶ This proprietary medicinal product is a second-line treatment, in patients who have been properly informed of the risks inherent in this practice, in certain forms of radiculalgia that have been present for several months and which are resistant to well-conducted medical treatments.

▶ There is a single therapeutic alternative with the same indication: HYDROCORTANCYL 2.5% suspension for injection (prednisolone).

Consequently, the actual benefit of ALTIM in the indication “in epidural injection: radiculalgia” is low.

The Committee recommends continued inclusion on the list of proprietary medicinal products refundable by National Health Insurance in the indication “in epidural injection: radiculalgia”.

▶ **Proposed reimbursement rate: 15%**

013 **TRANSPARENCY COMMITTEE RECOMMENDATIONS**

▶ **Packaging**

It is appropriate for the prescribing conditions according to the indication, the dosage, and the treatment duration.