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TRANSPARENCY COMMITTEE

Opinion

05 February 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 (2012):	H02AB17 (glucocorticoids)
Reason for the review	Renewal of inclusion
List concerned	National Health Insurance (French Social Security Code L.162-17)
Indications concerned	<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"

Actual Benefit	<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>
Improvement in Actual Benefit	-
Therapeutic use	-

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	Initial date (national): 30/12/1997
Prescribing and dispensing conditions/special status	List I

ATC Classification	2012 H insulins H02 H02A H02AB H02AB17	Systemic hormonal preparations, excl. sex hormones and Corticosteroids for systemic use Corticosteroids for systemic use, plain Glucocorticoids Cortivazol
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02 BACKGROUND

Review of the proprietary medicinal product included again on the list of medicines refundable by National Health Insurance for a period of 5 years starting on 31/12/2008 (Official Gazette of 12 May 2009).

On 19 November 1999, as part of the re-assessment of the actual benefit of ALTIM, the Committee concluded that the actual benefit of this proprietary medicinal product was "substantial" and specified that: "The epidural injections had marginal use and they do not provide any actual benefit".

On 26 November 2008, in its last opinion within the context of the renewal of inclusion, the Committee concluded that "The actual benefit of this proprietary medicinal product remains substantial in the Marketing Authorisation indications".

03 CHARACTERISTICS OF THE MEDICINAL PRODUCT

03.1 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"

03.2 Dosage

Equivalent anti-inflammatory (equal potency) doses for 5 mg prednisone = 0.3 mg cortivazol.

LOCAL ADMINISTRATION VIA INJECTION Do not administer intravenously or intramuscularly.

Shake before use.

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.

It is useless:

- to perform more than two injections in the first week,
- to perform a series of more than four injections.

Performing an injection that is too superficial should be avoided because of the risk of subcutaneous atrophy.

The injection will only be repeated if symptoms reappear or persist.

This proprietary medicinal product is not suitable for inhalation with a nebuliser.

04 ANALYSIS OF THE NEW DATA AVAILABLE

04.1 Efficacy

Among the data submitted, the company has provided a new clinical efficacy study¹ of CT-guided ductal and foraminal injections of corticosteroids in the treatment of radiculalgia caused by radicular disk herniation, focusing on 70 patients with radiculalgia resistant to appropriate drug treatment. As a retrospective, non-comparative study, its results have not been able to be taken into account within the context of this record.

04.2 Safety/Adverse effects

► The company has provided new safety data (PSUR covering the period from 01/05/2007 to 30/04/2010 and the period from 01/05/2010 to 30/04/2012).

► In October 2008, an official drug safety survey was carried out on the neurological adverse effects after CT-guided injections of glucocorticoid suspensions into the lumbar and cervical spine following the occurrence of cases of paraplegia/tetraplegia after CT-guided foraminal (i.e. intra-foraminal) or peri-radicular injections in rheumatological diseases.^{2,3}

This survey showed:

- a higher risk of spinal cord infarction after CT-guided foraminal lumbar injection into a spine that has undergone surgery. In patients with a history of lumbar spine surgery, these complications have also been observed after epidural and facet joint injection;
- a potentially fatal risk of stroke and spinal cord infarction after injection into the cervical spine.

All the complications were reported with HYDROCORTANCYL injection (prednisolone), but, because of the practitioners' habits, it seems that this product has almost exclusively been used for CT guided cortisone spine injections. As a result, there are no available data allowing the innocuousness of ALTIM to be established.²

► Changes have been made to the SPC since the last assessment by the Committee: an amendment to the Marketing Authorisation of 19 July 2010 was made following the results of the official drug safety survey relating to the cases of serious neurological complications (paraplegia, tetraplegia, cerebral infarction) reported following CT-guided glucocorticoid injections into the lumbar spine (epidural, foraminal or peri-radicular route) and cervical spine, as well as the application for changes requested by the company on 14 January 2009.

The following sections in particular have been changed (see amendment table in the appendix detailing all the changes):

Section 4.3 "Contraindications": addition of the following indication:

- epidural injection in patients with severe coagulation disorders or who are being treated with anticoagulants, ticlopidine, clopidogrel, other platelet aggregation inhibiting drugs or anti-thrombotic agents.

¹ Riboud C et al. Evaluation de l'efficacité des infiltrations canalaires et foraminales de corticoïdes guidées par TDM dans le traitement des radiculalgies par conflit disco radiculaire. J Radiol 2008; 89: 775-82.

² 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. Report for the National Pharmacovigilance Committee 27/01/2009.

³ AFSSAPS [French agency for the safety of healthcare products]. Risque de paraplégie/tétraplégie lié aux injections radioguidées de glucocorticoïdes au rachis lombaire ou cervical. Update. March 2011.

Section 4.4 "Special warnings and precautions for use": addition of the following entries:

- Warning specific to epidural administration: the following elements have been identified as risk factors for serious neurological undesirable effects: CT-guided foraminal injection, injection into a spine that has undergone surgery.

Section 4.8 "Undesirable effects":

Addition of the following entries:

- Allergic reactions: localised or generalised urticaria.

- Undesirable effects specific to epidural administration:

Transitory exacerbation of pain that led to the injection.

Undesirable effects resulting from a breach of the dura mater: orthostatic headaches, infectious or aseptic meningitis, cerebral venous thrombosis.

Administration into the cervical spine using the CT-guided foraminal route: very rare, sometimes fatal cases of cerebral or spinal cord infarction with tetraplegia.

Administration into the lumbar spine: very rare cases of spinal cord infarction with tetraplegia, mainly observed either via the CT guided foraminal route, or via various routes into a spine that has undergone surgery.

Epidural haematoma or infections (abscess, epiduritis), with a risk of acute spinal cord or radicular compression depending on the level.

► In view of these elements, since the last ALTIM review by the Transparency Committee, the safety profile of this proprietary medicinal product in the "epidural injection: radiculalgia" indication has changed. The known safety profile of this proprietary medicinal product in the other indications has not changed.

04.3 Usage/prescription data

It should be noted that, at the start of 2012, Sanofi had difficulties with the production of the proprietary medicinal product ALTIM (cortivazol), limiting the availability of this medicinal product to retail pharmacies and hospitals, increased by the concomitant stock depletion DIPROSTONE.⁴ These difficulties led to the establishment by Sanofi of a unit dose drug distribution system for ALTIM available, so as to avoid any complete interruption of supply. In this context and in agreement with the ANSM [National Medicines and Health Products Safety Agency], an information letter was sent by Sanofi to all healthcare professionals concerned informing them of this situation and inviting them to restrict as far as is possible the use of this proprietary medicinal product to clinical situations for which there are no treatment alternatives. Since 17 June 2013, ALTIM has been re-supplied to retail pharmacies with a unit dose drug distribution system and the distribution is normal in hospitals.⁵

The company has provided usage data for ALTIM extracted from an IMS Health Permanent Survey of Medical Prescription panel (moving annual total 2012 - Autumn 2012) according to which the annual number of prescriptions is estimated to be 1,064,000.

The majority of the patients treated are women (62%).

The indications at the beginning of the prescription for ALTIM mainly relate to diseases of the bones and joints, muscles and conjunctive tissue (88.9%).

The main co-prescriptions come within the scope of treatment of diseases corresponding to the indications of ALTIM.

ALTIM is prescribed as one injection a day (72% of prescriptions). For less than 1% of prescriptions, ALTIM is prescribed as two injections a day. For 28% of prescriptions, this information is not specified.

⁴ ANSM. Difficultés d'approvisionnement des corticoïdes injectables Altim® et Diprostene® - Point d'information. 22 May 2012.

⁵ ANSM. ALTIM 3,75 mg/1,5 ml, suspension injectable en seringue pré-remplie (cortivazol) - Remise à disposition. 25 June 2013.

For 15% of prescriptions, it is a one-day treatment. The prescriptions renewed at intervals of 7, 14 or 30 days represent 5% of prescriptions. Almost 80% of prescriptions do not mention the prescription period.

According to the data from the IMS Health Permanent Survey and Medical Prescription panel (moving annual total 2013 Autumn 2013), ALTIM was prescribed approximately 876,000 times.

04.4 Therapeutic use

The scientific data acquired on these rheumatological diseases and their treatment methods have also been taken into account:

- In intra-articular injection: inflammatory arthritis, advanced osteoarthritis.^{6,7,8,9,10,11}
- In periarticular injection: tendinitis, bursitis.^{12,13}
- In injection of soft tissue: talalgia, carpal tunnel syndrome, Dupuytren's contracture.^{14,15}
- In epidural injection: radiculalgia.¹⁶

⁶ Haute Autorité de Santé. Polyarthrite rhumatoïde. Rheumatoid arthritis: Medical, social and organisational aspects of treatment (excluding surgery and drugs) March 2007.

⁷ Zhang W et al., EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). EULAR evidence based recommendations for the management of hip osteoarthritis: report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis.* 2005 May; 64(5): 669-81.

⁸ Zhang W et al., EULAR evidence based recommendations for the management of hand osteoarthritis: report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis.* 2007 Mar; 66(3): 377-88.

⁹ Jordan KM et al., Standing Committee for International Clinical Studies Including Therapeutic Trials ESCISIT. EULAR Recommendations 2003: an evidence based approach to the management of knee osteoarthritis: Report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). *Ann Rheum Dis.* 2003 Dec; 62(12): 1145-55.

¹⁰ Hameed F, Ihm J. Injectable medications for osteoarthritis. *PM R.* 2012 May; 4(5 Suppl): S75-81.

¹¹ Combe B et al., EULAR recommendations for the management of early arthritis: report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis.* 2007 Jan; 66(1): 34-45.

¹² Ashraf MO, Devadoss VG. Systematic review and meta-analysis on steroid injection therapy for de Quervain's tenosynovitis in adults. *Eur J Orthop Surg Traumatol.* 2013 Jan 22.

¹³ HAS, Prise en charge chirurgicale des tendinopathies rompues de la coiffe des rotateurs de l'épaule chez l'adulte, 2008.

¹⁴ Gelfman R, Melton LJ, Yawn BP, Wollan PC, Amadio PC, Stevens JC. Long-term trends in carpal tunnel syndrome. *Neurology* 2009; 72(1): 33-36.

¹⁵ Agence nationale d'accréditation et d'évaluation en santé. Stratégie des examens paracliniques et des indications thérapeutiques dans le syndrome du canal carpien. Paris: ANAES [National Health Accreditation and Assessment Agency]; 1997.

¹⁶ Wybier M. Infiltrations épidurales et foraminales lombaires : mise au point. *J Radiol* 2010; 91: 1079-85.

05 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee's opinion is that the conclusions of its previous opinion of 26 November 2008 are not to be changed in the indications for intra-articular injection, periarticular injection, and injection of soft tissue:

05.1 Actual benefit

In intra-articular injection: inflammatory arthritis

- ▶ The condition treated with this proprietary medicinal product is characterised by progression to disability and/or a marked deterioration in quality of life.
- ▶ This proprietary medicinal product is intended as symptomatic therapy.
- ▶ The efficacy/adverse effects ratio is substantial.
- ▶ Alternative pharmacological and non-pharmacological products exist.
- ▶ This medicinal product is a first-line therapy.

- In intra-articular injection: advanced osteoarthritis.

- ▶ The condition treated with this proprietary medicinal product is characterised by progression to disability and/or a marked deterioration in quality of life.
- ▶ This proprietary medicinal product is intended as symptomatic therapy.
- ▶ The efficacy/adverse effects ratio is modest.
- ▶ Alternative pharmacological and non-pharmacological products exist.
- ▶ This medicinal product is a second-line therapy.

- In periarticular injection: tendinitis, bursitis.

- ▶ The condition treated with this proprietary medicinal product is not life-threatening for the patient, nor does it cause serious complications, any disability, or a marked deterioration in quality of life.
- ▶ This proprietary medicinal product is intended as symptomatic therapy.
- ▶ The efficacy/adverse effects ratio is modest.
- ▶ Alternative pharmacological and non-pharmacological products exist.
- ▶ This medicinal product is a second-line therapy.

- In injection of soft tissue: talalgia, carpal tunnel syndrome, Dupuytren's contracture.

- ▶ The condition treated with this proprietary medicinal product is characterised by progression to disability and/or a marked deterioration in quality of life.
- ▶ This proprietary medicinal product is intended as symptomatic therapy.
- ▶ The efficacy/adverse effects ratio is modest.
- ▶ Alternative pharmacological and non-pharmacological products exist.
- ▶ This medicinal product is a second-line therapy.

Consequently, the Committee considers that the actual benefit of ALTIM remains substantial 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.

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.

05.2 Transparency Committee recommendations

The Committee recommends continued inclusion on the list of medicines refundable by National Health Insurance in the indications in the Marketing Authorisation for 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.

The Committee does not make any comment on the continued inclusion on the list of medicines refundable by National Health Insurance in the indication "in epidural injection: 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.

▶ **Proposed reimbursement rate: 65%**

▶ **Packaging**

Appropriate for the prescription conditions as regards the indication, dosage and treatment duration.

Appendix: changes to the SPC

<u>SPC wording of 10/11/2006</u>	<u>Changes to the SPC</u> (Marketing Authorisation amendments of 19/07/2010)
4. CLINICAL PARTICULARS	4. CLINICAL PARTICULARS
4.2 Posology and method of administration	4.2 Posology and method of administration
<p>Equivalent anti-inflammatory (equal potency) doses for 5 mg prednisone = 0.3 mg cortivazol.</p> <p>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).</p> <p>NB:</p> <ul style="list-style-type: none"> • Do not use more than 1.5 ml per session no matter how many joints are injected. <p>It is useless:</p> <ul style="list-style-type: none"> • to perform more than two injections in the first week, • to perform a series of more than four injections. <p>The injection will not be repeated if symptoms reappear or persist. This proprietary medicinal product is not suitable for being inhaled with a nebuliser.</p>	<p>Equivalent anti-inflammatory (equal potency) doses for 5 mg prednisone = 0.3 mg cortivazol, LOCAL ADMINISTRATION VIA INJECTION Do not administer intravenously or intramuscularly. Shake before use.</p> <p>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).</p> <p>NB:</p> <ul style="list-style-type: none"> • Do not use more than 1.5 ml per session no matter how many joints are injected. <p>It is useless:</p> <ul style="list-style-type: none"> • to perform more than two injections in the first week, • to perform a series of more than four injections. <p>Performing an injection that is too superficial should be avoided because of the risk of subcutaneous atrophy.</p> <p>The injection will only be repeated if symptoms reappear or persist. This proprietary medicinal product is not suitable for being inhaled with a nebuliser.</p>
4.3 Contraindications	4.3 Contraindications

<p style="text-align: center;"><u>SPC wording of 10/11/2006</u></p>	<p style="text-align: center;"><u>Changes to the SPC</u> (Marketing Authorisation amendments of 19/07/2010)</p>
<p>This medicinal product is contraindicated in the following situations:</p> <ul style="list-style-type: none"> • local or general infection, or suspected infection, • severe coagulation disorders, anticoagulant treatment under way, • hypersensitivity to one of the ingredients, • via the intradiscal route of administration. 	<p>This medicinal product is contraindicated in the following situations:</p> <ul style="list-style-type: none"> • local or general infection, or suspected infection, • severe coagulation disorders, anticoagulant treatment under way, • epidural injection in patients with severe coagulation disorders or who are being treated with anticoagulants, ticlopidine, clopidogrel, other anti-platelet drugs or anti-thrombotic agents. • hypersensitivity to one of the ingredients, • via the intradiscal route of administration. • because of the presence of benzyl alcohol, this medicinal product is contraindicated in premature babies and newborn babies who are born to term.
<p>4.4 Special warnings and precautions for use</p>	<p>4.4 Special warnings and precautions for use</p>
<p>Warnings</p>	<p>Special warnings</p>
<p>Because of a potential systemic distribution, certain contraindications of corticosteroids via the general route must be taken into account, in particular if the injections are multiple (several locations) or repeated in the short-term:</p> <ul style="list-style-type: none"> • some evolving viruses (in particular hepatitis, herpes, chickenpox, shingles), • psychotic states not yet controlled by treatment, • live vaccines. <p>Corticosteroid treatment may promote the occurrence of various infectious complications.</p> <p>Multiple injections (several locations) or ones repeated in the short-term may cause clinical and biological symptoms of Cushing's syndrome.</p> <p>Attention is drawn to athletes as this proprietary medicinal product contains an active substance which can induce a positive reaction in tests performed during anti-doping controls.</p> <p>Concomitant intake of cortivazol with sultopride or live attenuated vaccines is not recommended (see section 4.5).</p> <p>Oral or injectable corticosteroids may promote the onset of tendinopathy, even tendon rupture (uncommon). This risk is increased when there is a co-prescription for fluoroquinolones and in patients on dialysis with secondary</p>	<p>Because of a potential systemic distribution, certain contraindications of corticosteroids via the general route must be taken into account, in particular if the injections are multiple (several locations) or repeated in the short-term:</p> <ul style="list-style-type: none"> • some evolving viruses (in particular hepatitis, herpes, chickenpox, shingles), • psychotic states not yet controlled by treatment, • live vaccines. <p>Corticosteroid treatment may promote the occurrence of various infectious complications.</p> <p>Multiple injections (several locations) or ones repeated in the short-term may cause clinical and biological symptoms of Cushing's syndrome as well as attenuation of the hypothalamic-pituitary-adrenal axis.</p> <p>Attention is drawn to athletes as this proprietary medicinal product contains an active substance which can induce a positive reaction in tests performed during anti-doping controls.</p> <p>The concomitant administration of cortivazol which was carried out with sultopride or live attenuated vaccines or acetylsalicylic acid used in anti inflammatory doses (≥ 1 g per dose and/or ≥ 3 g a day) is not recommended (see section 4.5).</p> <p>Oral or injectable corticosteroids may promote the onset of tendinopathy, even tendon rupture (uncommon). They should therefore not be injected intra-</p>

<u>SPC wording of 10/11/2006</u>	<u>Changes to the SPC</u> <u>(Marketing Authorisation amendments of 19/07/2010)</u>
hyperparathyroidism or who have undergone a kidney transplant.	tendinously. This risk is increased when there is a co-prescription for fluoroquinolones and in patients on dialysis with secondary hyperparathyroidism or who have undergone a kidney transplant. It seems that in cases of allergic reaction, the allergen responsible is most often carmellose, the suspension agent. This medicinal product contains 13.50 mg of benzyl alcohol per 1.5 ml pre-filled syringe. It may cause toxic reactions and anaphylactoid reactions in breast feeding babies and children up to the age of 3. This medicinal product contains sodium. The sodium level is less than 1 mmol per dose, i.e. "sodium-free".
	Warnings specific to epidural administration:
	The following elements have been identified as risk factors for serious neurological undesirable effects: CT-guided foraminal injection, injection into a spine that has undergone surgery.
Special precautions for use	Special precautions for use
<ul style="list-style-type: none"> • It is necessary to observe strict asepsis. • Local injection of corticosteroids may destabilise diabetes, a psychotic state or severe hypertension. • Administration should be carried out with care in patients with a high risk of infection, particularly in the case of those who have had haemodialysis or who are prosthesis wearers. • Do not inject intra-tendinously. 	<ul style="list-style-type: none"> • It is necessary to observe strict asepsis. • Local injection of corticosteroids may destabilise diabetes, a psychotic state or severe hypertension. • Administration should be carried out with care in patients with a high risk of injection, particularly in the case of those who have had haemodialysis or who are prosthesis wearers. • The risk of a vasomotor reaction and in particular chest pain is to be taken into account in patients who have underlying progressive cardiovascular disease. • Do not inject intra-tendinously because of the risk of rupture. • Do not administer intravenously or intramuscularly. • This proprietary medicinal product is not suitable for being inhaled with a nebuliser.
4.5 Interaction with other medicinal products and other forms of interaction	4.5 Interaction with other medicinal products and other forms of interaction <i>Update with the thesaurus of drug interactions in force for glucocorticoids.</i>
4.8 Undesirable effects	4.8 Undesirable effects

<p style="text-align: center;"><u>SPC wording of 10/11/2006</u></p>	<p style="text-align: center;"><u>Changes to the SPC</u> (Marketing Authorisation amendments of 19/07/2010)</p>
<p>The systemic undesirable effects of glucocorticoids have a low risk of occurrence after local administration, taking into account low blood levels. However, the risk of Cushing's syndrome (salt and water retention, uncontrolled diabetes and hypertension...) increases with the dose and frequency of injections.</p> <ul style="list-style-type: none"> • risk of local infection (depending on the injection site): arthritis, meningitis, • localised atrophy of muscles, subcutaneous and cutaneous tissue, risk of tendon rupture in the event of injection into the tendons, • some cases of tendon ruptures have been described as uncommon occurrences, in particular when co-prescribed with fluoroquinolones, • early-onset acute arthritis due to microcrystals (with microcrystalline suspension), • local calcifications, • local and systemic allergic reactions: cutaneous, uncommonly, Quincke's oedema, anaphylactic shock, • flush: headaches and flushing can occur, They usually disappear in 1 or 2 days, • transient low back pain, uncommonly: chest pain, • blood pressure surges, uncommonly: hypotension, • pain at the injection site. 	<p>The systemic undesirable effects of glucocorticoids have a low risk of occurrence after local administration, taking into account low blood levels. However, the risk of Cushing's syndrome (salt and water retention, uncontrolled diabetes and of hypertension...) as well as attenuation of the hypothalamic-pituitary-adrenal axis increases with the dose and frequency of injections.</p> <p>Undesirable effects common to all routes of administration:</p> <ul style="list-style-type: none"> • risk of local infection (depending on the injection site): arthritis, meningitis, epiduritis, • localised atrophy of muscles, subcutaneous and cutaneous tissue, risk of tendon rupture in the event of injection into the tendons <small></pt623,</small> • some cases of tendon ruptures have been described as uncommon occurrences, in particular when co-prescribed with fluoroquinolones, • early-onset acute arthritis due to microcrystals (with microcrystalline suspension), • local calcifications, • local and systemic allergic reactions: cutaneous, localised or generalised urticaria, uncommonly, Quincke's oedema, anaphylactic shock, • flush: headaches and flushing can occur. They usually disappear in 1 or 2 days, • Transient low back pain, uncommonly: chest pain, • lumbar pain, more rarely chest pain and/or hypotension occurring within minutes after the injection and spontaneously reversible, • blood pressure surges, uncommonly: hypotension, • pain at the injection site.

<p style="text-align: center;"><u>SPC wording of 10/11/2006</u></p>	<p style="text-align: center;">Changes to the SPC (Marketing Authorisation amendments of 19/07/2010)</p>
	<p>Undesirable effects specific to epidural administration:</p> <ul style="list-style-type: none"> • transitory exacerbation of pain that led to the injection, • undesirable effects resulting from a breach of the dura mater: orthostatic headaches, infectious or aseptic meningitis, cerebral venous thrombosis, • administration into the cervical spine using the CT-guided foraminal route: very rare, sometimes fatal cases of cerebral or spinal cord infarction with tetraplegi, • administration into the lumbar spine: very rare cases of spinal cord infarction with paraplegia, mainly observed either via the CT guided foraminal route, or via various routes into a spine that has undergone surgery, • epidural haematoma or infections (abscess, epiduritis), with risk of acute spinal cord or radicular compression depending on the level.
<p>4.9 Overdose Not applicable.</p>	<p>4.9 Overdose With corticosteroid treatment administered via the general route the following may be observed:</p> <ul style="list-style-type: none"> - Clinical signs: excess weight, obesity, muscle atrophy, digestive disorders, osteoporosis, AHT, hypertrichosis, purpura, acne, - Neuropsychiatric signs: excitement, agitation, - Endocrinal and metabolic signs: true iatrogenic Cushing's syndrome, stunted growth in children, - Biological signs: glycosuria, hyperglycaemia, hypokalaemia.