TRANSPARENCY COMMITTEE

Opinion

29 November 2006

HEXATRIONE 2% suspension for injection (intra-articular)
Box containing one 2-ml vial - CIP code: 318 413-0

Applicant: SANKYO PHARMA FRANCE

Triamcinolone hexacetonide

List I

Marketing authorisation date: December 30, 1997

Date of most recent modification of Marketing Authorisation: March 31, 2006 (extension of indication in children: juvenile idiopathic arthritis)

Reason for request: Inclusion on the list of medicines reimbursed by French National Health Insurance and approved for use by hospitals in the extension of indication "juvenile idiopathic arthritis"
1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
Triamcinolone hexacetonide

1.2. Background
First local corticoid to obtain Marketing Authorisation (MA) in the treatment of juvenile idiopathic arthritis.

1.3. Indications
The same as those of local corticotherapy where the condition justifies a strong local concentration. All prescriptions for local injections must refer to the danger of infection, particularly the risk of encouraging bacterial proliferation.

This medicinal product is indicated for intra-articular injection in rheumatological disorders: inflammatory arthritis (adult forms, juvenile idiopathic arthritis in infants aged at least one year, in children and adolescents), exacerbations of osteoarthritis.

1.4. Dosage
INTRA-ARTICULAR ADMINISTRATION ONLY

Anti-inflammatory equivalence (equipotency) for 5 mg of prednisolone = 4 mg of triamcinolone.

**Adults:** from 0.5 to 2 ml of suspension depending on the size of the joint, i.e. 10 to 40 mg of triamcinolone hexacetonide **without exceeding two ampoules of 40 mg.** Care should be taken to ensure that the injection is sufficiently deep because of the risk of skin atrophy. Injection should only be repeated in the case of recurrence or persistence of symptoms.

**Infants (> 1 year), children and adolescents:** Administration is reserved for practitioners with experience in the treatment of the disease. The dose must be adjusted according to the size of the joint in order to avoid any back diffusion liable to cause peri-articular calcification and skin atrophy.

The usual recommended dose is 5 mg (0.25 ml) to 40 mg (2 ml) per injection. Do not exceed the dose of 40 mg per injection.

Injections should only be repeated in the case of recurrence or persistence of symptoms, after a minimal period of from 3 to 6 months after the last administration.

The ampoule must be shaken before use.

This medicinal product is not suitable for administration by the inhaled route with a nebulizer.
2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC classification (2005)
H : Systemic hormonal preparations, excluding sex hormones and insulins
02 : Corticosteroids for systemic use
A : Corticosteroids for systemic use, plain
B : Glucocorticoids
08 : Triamcinolone

2.2. Medicines in the same therapeutic category
Comparator medicines
No other injectable corticosteroid has been granted an MA specifically for juvenile idiopathic arthritis in infants aged at least one year.

However, there are other local injectable corticosteroids which are indicated for inflammatory arthritis (betamethasone, prednisolone, methylprednisolone, triamcinolone acetonide, cortivazol) without any indication as to whether they can be used in children, apart from KENACORT Retard which is contraindicated in children under three as it contains benzyl alcohol. Nevertheless, there is no absolute contraindication for corticosteroid treatment administered to preserve life. Please note that Hexatrione also contains benzyl alcohol.

2.3. Medicines with a similar therapeutic aim
Other symptomatic treatments: NSAIDs and corticosteroids administered via a general route.

3. ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The dossier submitted by the company for the medicinal product HEXATRIONE in the new indication "juvenile idiopathic arthritis (JIA)" is based on bibliographical data and comprises three comparative studies and four non-comparative studies.

As little clinical information is available for this paediatric condition, all the studies presented will be described despite their methodological shortcomings:

- Three controlled studies comparing the medicinal product with other injectable glucocorticosteroids which do not have an MA specifically for use in children: betamethasone and triamcinolone acetonide.

Balogh (1988)¹
Randomised double-blind study comparing an intra-articular injection into the knee of triamcinolone hexacetonide (n=11) or betamethasone (n=12) at an unspecified fixed dose in 23 children with an oligoarticular form of JIA and an average age of 10.3 years (5-16).

The efficacy evaluation endpoint were:
- The condition of the joint evaluated by measuring the circumference of the knee and the degree of flexion on D1, D3, D7 and D42 after the injection.
- The patient’s overall assessment of response to treatment using a four-point scale (excellent = 1, satisfactory = 2, moderate = 3, poor = 4) on D1, D7 and D42.

No primary endpoint has been defined.

Results

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Betamethasone (n=12)</th>
<th>Triamcinolone hexacetonide (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Circumference of the knee (cm)</td>
<td>On inclusion 30.8±5.6</td>
<td>32.5±4.9</td>
</tr>
<tr>
<td></td>
<td>D7 30.5±5.0</td>
<td>30.6±4.6</td>
</tr>
<tr>
<td></td>
<td>D42 31.8±4.6</td>
<td>30.8±4.2</td>
</tr>
<tr>
<td>Knee flexion (degree)</td>
<td>On inclusion 130±12</td>
<td>131±6</td>
</tr>
<tr>
<td></td>
<td>D7 134±11</td>
<td>142±8</td>
</tr>
<tr>
<td></td>
<td>D42 130±16</td>
<td>144±9</td>
</tr>
</tbody>
</table>

Conclusion:
It is impossible to characterise the quantitative effect of triamcinolone hexacetonide in view of the methodological shortcomings of this study, in particular:
- The lack of a defined primary endpoint;
- The multiple evaluation criteria;
- The small population size.

Zulian (2003)²
Open-label comparative study of triamcinolone hexacetonide and triamcinolone acetonide (Kenacort retard®) in 85 patients with an average age of 5 years suffering from an oligoarticular form of JIA.

A total of 130 joints were treated with an injection of either triamcinolone hexacetonide (70 injections) or triamcinolone acetonide (60 injections) at a dose of 1 mg/kg (maximum dose: 40 mg) in line with treatment availability.

The primary endpoint was the articular score assessed 6, 12 and 24 months after the injection.

The study also evaluated:
- The proportion of patients who responded in a satisfactory manner, defined by absence of signs of synovitis or a fall of at least 60% in the articular score,
- The relapse rate.

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Results
- No data on change of the articular score (principal criterion) are available.
- Triamcinolone hexacetonide performed better than triamcinolone acetonide when judged by the satisfactory response rate after 6, 12 and 24 months.

<table>
<thead>
<tr>
<th>Satisfactory response rate at</th>
<th>Triamcinolone hexacetonide</th>
<th>Triamcinolone acetonide</th>
<th>difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months</td>
<td>81.4%</td>
<td>53.3%</td>
<td>p = 0.001</td>
</tr>
<tr>
<td>12 months</td>
<td>67.1%</td>
<td>43.3%</td>
<td>p = 0.006</td>
</tr>
<tr>
<td>24 months</td>
<td>60%</td>
<td>33.3%</td>
<td>p = 0.002</td>
</tr>
</tbody>
</table>

- The relapse risk was higher in the group treated with triamcinolone acetonide than in the group treated with triamcinolone hexacetonide (RR: 2.5 [1.4-4.4] at 6 months, 1.7 [1.2-2.6] at 12 months and 1.7 [1.2-2.3] at 24 months).

**Zulian F, Italy (2004)**
Randomised, double-blind study comparing triamcinolone hexacetonide and triamcinolone acetonide in 37 children with an average age of 4.9 years (1.1 - 14.8), 32 of whom were suffering from an oligoarticular form of JIA and five of whom had a polyarticular form of the condition.

A total of eighty-six joints were treated either with triamcinolone hexacetonide (43 injections) at a dose of 1 mg/kg (maximum dose: 40 mg) or triamcinolone acetonide (43 injections) at a dose of 2 mg/kg (maximum dose: 80 mg).

The primary endpoint was the articular score assessed 6, 12 and 24 months after the injection.

The study also evaluated:
- The proportion of patients who responded in a satisfactory manner, defined by absence of signs of synovitis or a fall of at least 60% in the articular score,
- The relapse rate.

Results:
- The change of the articular score (principal criterion) was not specified.
- The satisfactory relapse rate was higher in the triamcinolone hexacetonide group at 6, 12 and 24 months.

<table>
<thead>
<tr>
<th>Satisfactory response rate at</th>
<th>triamcinolone hexacetonide</th>
<th>triamcinolone acetonide</th>
<th>difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months</td>
<td>89.7%</td>
<td>61.5%</td>
<td>p = 0.008</td>
</tr>
<tr>
<td>12 months</td>
<td>84.6%</td>
<td>48.7%</td>
<td>p = 0.001</td>
</tr>
<tr>
<td>24 months</td>
<td>76.9%</td>
<td>38.5%</td>
<td>p = 0.001</td>
</tr>
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</table>

- The relapse rate after a monitoring period of two to twenty-four months was 15.4% in the triamcinolone hexacetonide group versus 53.8% in the triamcinolone acetonide group.


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Other data:
A retrospective subgroup analysis conducted by BREIT et al, 2000 on a series of 194 children (average age not specified) suffering from all forms of JIA (oligoarthritis in 60% of the cases) treated between 1989 and 1994 suggests that triamcinolone hexacetonide is effective for all forms of JIA. Furthermore, this subgroup analysis shows that improvement lasts longer in oligoarticular forms (121 weeks) and forms of polyarthritis without rheumatoid factors (105 weeks) than in forms of polyarthritis with rheumatoid factors (63 weeks), forms of spondylarthropathy (47 weeks) and systemic forms (36 weeks).

3.2. Adverse effects
The adverse effects most frequently reported in the studies were similar to those reported for adults: subcutaneous atrophy and joint calcifications. These are known adverse events associated with corticosteroids administered by injection. However, three cases of femoral head necrosis were reported in the clinical studies performed by NEIDEL (2 cases) and BREIT (1 case) in patients who were also receiving corticosteroid treatment by a general route at the same time. The outcome of these cases was not documented.

3.3. Conclusion
The efficacy of triamcinolone hexacetonide in the treatment of juvenile idiopathic arthritis, particularly the oligoarticular form (over 60% of cases) is based on eight clinical studies published between 1986 and 2004 and conducted on a total of 558 children who were monitored for 6 months to 24 months.

Three of these studies compared the product with another glucocorticosteroid: betamethasone or triamcinolone acetonide.

- In Balogh's study, conducted on a small population (23 children), triamcinolone hexacetonide administered at a non-specified dose was superior to betamethasone (dose not specified) for the following criteria: circumference of the knee, degree of flexion and the patient's overall assessment of the effect of treatment.

- In the two studies conducted by Zulian, no conclusion can be drawn from a comparison of 1 mg/kg of triamcinolone hexacetonide with 1 mg/kg or 2 mg/kg of triamcinolone acetonide as no results on the primary endpoint (articular score) are available.

The tolerance profile of this medicinal product in children was similar to that reported in adults. The most frequent adverse events were subcutaneous atrophy and joint calcification, but three cases of femoral head necrosis were reported in patients also receiving corticosteroid treatment by a general route at the same time.

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Experts regard HEXATRIONE as the standard local treatment for juvenile idiopathic arthritis in view of its longer duration of action. According to the experts, there is currently no better alternative in the same class.
**Non-comparative prospective studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Methodology</th>
<th>Follow-up</th>
<th>Population</th>
<th>Diagnosis and inclusion criteria</th>
<th>Treatment (dose and route of administration)</th>
<th>Evaluation criteria</th>
<th>Results (efficacy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allen RC.</td>
<td>Prospective uncontrolled</td>
<td>2 years</td>
<td>40 (31 girls and 9 boys) Average age not specified but &lt; 16 years</td>
<td>JIA according to ARA: oligoarticular (29) PR (6) seronegative polyarthritis (4) ankylosing spondylarthritis (1)</td>
<td>1 injection of TH in the knee (20 to 40 mg)</td>
<td>* Rate of response to treatment * Rate of relapse * Time to relapse Evaluation at 6, 12 and 24 months</td>
<td>* Rate of response - oligoarticular form 67.6% at 6 months and 50% at 1 year - other clinical forms 50% at 6 months and 30% at 1 year * Rate of relapse 8 knees were treated twice (5 favourable responses); 2 knees were treated three times and one knee was treated four times with a further relapse.</td>
</tr>
<tr>
<td>Earley A.</td>
<td>Prospective uncontrolled</td>
<td>1 year</td>
<td>60 (36 girls and 24 boys) Average age: 4.5 years [1.4-10]</td>
<td>JIA: oligoarthritis of the knee</td>
<td>1 injection of TH in the knee (20 mg if weight &lt; 20 kg and 40 mg if weight &gt; 20 kg)</td>
<td>Overall assessment of the response by the physician Evaluation at 3, 6 and 12 months</td>
<td>* Overall assessment at 1 year: good to excellent results in 77% of cases and 11 knees were re-injected (two were re-injected three times within 1 year).</td>
</tr>
<tr>
<td>Padeh S.</td>
<td>Prospective uncontrolled</td>
<td>5 years</td>
<td>71 (47 girls and 24 boys) Average age: 9.4 years [0.5-18]</td>
<td>Juvenile chronic arthritis according to ACR: all forms (including 43 oligoarticular) after failure of NSAID administered for 6 to 8 weeks</td>
<td>1 injection of intraarticular TH (10 to 40 mg depending on the size of the joint).</td>
<td>* Good response = disappearance of synovitis in the first week and no relapse at 6 months * Failure = relapse within 6 months Evaluation at 6 and 36 months</td>
<td>* 82% remission rate at 6 months (246/300 injections) * 38 children had only one injection; 18 children had two injections and 9 children had three injections at six-month intervals. 6 children had more than three injections.</td>
</tr>
<tr>
<td>Neidel J.</td>
<td>Prospective uncontrolled</td>
<td>2 years</td>
<td>48 (30 girls and 18 boys) Average age: 10 years [2-17]</td>
<td>Juvenile chronic arthritis according to ACR: coxitis</td>
<td>1 injection (follow-up) of TH in the hip (1 mg/kg up to a maximum of 40 mg)</td>
<td>Clinical remission of synovitis confirmed by echography and MRI after two years.</td>
<td>* 76% remission of coxitis * 58% remission of coxitis with a single injection in the two years of the study (39/67).</td>
</tr>
</tbody>
</table>

JIA: juvenile idiopathic arthritis, ACR: American College of Rheumatology, TH: triamcinolone hexacetonide, PR: psoriatic rheumatism, ARA: American Rheumatism Association

4.1. **Actual benefit**

Juvenile idiopathic arthritis designates all articular inflammatory conditions with no known cause that start before the age of 16 and last for more than 6 weeks\(^9\). These are serious and disabling chronic conditions.

This medicine is intended as symptomatic therapy.

**Public health benefit:**

The burden on public health caused by juvenile idiopathic arthritis is small because of the small number of patients affected (orphan condition).

Improving pain control (GTNDO\(^{10}\) pain) for this orphan disease ("rare diseases" plan) is an integral part of public health priorities.

The available data is insufficient to quantify the population impact of HEXATRIONE. However, the professional consensus that this is a better standard local treatment than other local treatments indicates that this medicinal product is likely to have a slight impact on the morbidity and quality of life of patients who undergo treatment.

HEXATRIONE is part of the response to the identified need to improve pain control in this orphan pathology of juvenile arthritis.

Therefore, the medicinal product HEXATRIONE has a public health benefit for this indication given the current state of knowledge. This interest is minor.

The efficacy/safety ratio for this medicinal product is high. It is a second-line treatment after anti-inflammatories administered by the general route and/or drugs treating an underlying condition have failed.

There is no local therapeutic alternative with an MA specifically for children.

The actual benefit for this indication is substantial.

**4.2. Improvement in actual benefit**

In the indication "juvenile idiopathic arthritis in infants aged at least one year, in children and in adolescents", HEXATRIONE® provides a moderate (IAB III) improvement in actual benefit in the strategy of addressing this condition.

**4.3. Therapeutic use \(^{9,11,12}\)**

The aim of the treatment is to combat inflammation, relieve pain and stiffness and prevent or slow down articular lesions.

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\(^{10}\) GTNDO is the national technical objective definition group

\(^{11}\) Hull RG; British Paediatric Rheumatology Group. Guidelines for management of childhood arthritis. Rheumatology 2001 ; 40 (11) : 1309-12

\(^{12}\) Hashkes PJ, Laxer RM. Medical treatment of juvenile idiopathic arthritis. JAMA 2005 ; 294(13) : 1671-84
It makes use of fast-acting symptomatic treatments (NSAIDs, corticosteroids) and sometimes long-term treatments (particularly methotrexate or etanercept in patients who do not respond to methotrexate) depending on the form which the juvenile idiopathic arthritis takes (systemic, oligoarticular or polyarticular).

NSAIDs are usually the first-line treatment, but they are not always effective.

Experts believe that HEXATRIONE is an essential medicinal product in the control of juvenile idiopathic arthritis because of its long duration of action, especially for local treatment of oligoarticular forms, which are the most common clinical form of the condition, but also for polyarticular forms, as a complement to other treatments (particularly long term). The recommended dose is 0.5 to 1 mg/kg/joint depending on the size of the joint. Further doses should only be injected if the symptoms reappear or persist, leaving at least three to six months between injections.

4.4. Target population

It is thought that around 3,000 children under 16 in France suffer from juvenile idiopathic arthritis13,14.

Experts believe that around one third of these patients will undergo at least one corticosteroid injection in childhood, giving a target population for HEXATRIONE of 1,000 patients.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for use by hospitals and various public services in the new indication and at the posology in the marketing authorisation.

4.5.1 Packaging: Appropriate for the prescription conditions

4.5.2 Reimbursement rate: 65%