XALUPRINE 20 mg/ml, oral suspension
B/1 bottle (CIP: 34009 224 574 0 6)

Applicant: LUCANE PHARMA

<table>
<thead>
<tr>
<th>INN</th>
<th>mercaptopurine</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATC Code (2013):</td>
<td>L01BB02 (purine analogues)</td>
</tr>
<tr>
<td>Reason for the request</td>
<td>Inclusion</td>
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<tr>
<td>Lists concerned</td>
<td>National Health Insurance (French Social Security Code L.162-17)</td>
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<td></td>
<td>Hospital use (French Public Health Code L.5123-2)</td>
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<tr>
<td>Indication concerned</td>
<td>&quot;Xaluprine is indicated for the treatment of acute lymphoblastic leukaemia (ALL) in adults, adolescents and children.&quot;</td>
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<tr>
<td><strong>Actual Benefit</strong></td>
<td>The actual benefit of XALUPRINE is substantial in the Marketing Authorisation indication.</td>
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</tr>
<tr>
<td><strong>Improvement in Actual Benefit</strong></td>
<td>XALUPRINE provides a minor improvement in actual benefit (IAB IV) compared with mercaptopurine in tablet form in the treatment of acute lymphoblastic leukaemia in children (paediatric population). In adults and adolescents, XALUPRINE does not provide any improvement in actual benefit (IAB V, non-existent) compared with mercaptopurine in tablet form in the treatment of acute lymphoblastic leukaemia.</td>
</tr>
<tr>
<td><strong>Therapeutic use</strong></td>
<td>Mercaptopurine oral suspension (XALUPRINE) treatment mainly falls within the scope of maintenance treatment of acute lymphoblastic leukaemia in the paediatric population.</td>
</tr>
</tbody>
</table>
1 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (centralised procedure) | Date initiated: 2 March 2012
---|---
Prescribing and dispensing conditions / special status | List I
- Medicine for hospital prescription restricted to haematologists or doctors trained in blood diseases.
- Medicine requiring special monitoring during treatment.
- Orphan medicinal product

ATC Classification

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>2013</td>
<td>Antineoplastic and immunomodulating agents</td>
</tr>
<tr>
<td>L01</td>
<td>Antineoplastic agents</td>
</tr>
<tr>
<td>L01B</td>
<td>Antimetabolites</td>
</tr>
<tr>
<td>L01BB</td>
<td>Purine analogues</td>
</tr>
<tr>
<td>L01BB02</td>
<td>Mercaptopurine</td>
</tr>
</tbody>
</table>

2 BACKGROUND

Review of the application for inclusion of the proprietary medicinal product XALUPRINE 20 mg/ml, oral suspension on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use.

Mercaptopurine has been distributed as a "special preparation" in the United Kingdom for 10 years. The "special preparations" are made specifically for individualised patients under special authorisation. About 65,000 units have been distributed to almost 300 hospitals in the United Kingdom and Ireland over 9 years. It is thus estimated that more than 2,500 children have been treated with the mercaptopurine oral suspension formulation.

3 THERAPEUTIC INDICATION

"Xaluprine is indicated for the treatment of acute lymphoblastic leukaemia (ALL) in adults, adolescents and children."

4 DOSAGE

"Xaluprine treatment should be supervised by a physician or other healthcare professional experienced in the management of patients with ALL."

Posology

The dose is governed by close monitoring of the haematotoxicity and should be carefully adjusted to suit the individual patient in accordance with the employed treatment protocol. Depending on phase of treatment, starting or final doses generally vary between 25 and 75 mg/m² body surface area (BSA) per day, but should be lower in patients with reduced or absent thiopurine methyltransferase (TPMT) enzyme activity (see section in the SPC)."
5 **THERAPEUTIC NEED**

This application concerns a medicinal product where the active ingredient mercaptopurine has been used long-term in the curative treatment of acute lymphoblastic leukaemia (ALL) in tablet form only (data of licence: 19/07/1954), making it difficult to adjust the dose in younger children. The current oral suspension formulation allows appropriate use in the paediatric population.

6 **CLINICALLY RELEVANT COMPARATORS**

6.1 Medicinal products

The comparator of XALUPRINE is the other galenic form of mercaptopurine available in tablet form at a dose of 50 mg (PURINETHOL).

**Conclusion**

There is no relevant comparator for XALUPRINE in this indication.

7 **INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT**

<table>
<thead>
<tr>
<th>Country</th>
<th>REIMBURSEMENT</th>
<th>Population(s)</th>
</tr>
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<tbody>
<tr>
<td>Several countries of the EU including Germany, Denmark, Italy, Sweden and Norway</td>
<td>Yes</td>
<td>MA population</td>
</tr>
<tr>
<td>Australia</td>
<td>Submission in progress</td>
<td>Acute Lymphoblastic Leukaemia</td>
</tr>
<tr>
<td>USA</td>
<td>Assessment in progress</td>
<td>Acute Lymphoblastic Leukaemia</td>
</tr>
</tbody>
</table>
8 Analysis of Available Data

6-mercaptopurine has been used for the treatment of acute lymphoblastic leukaemia (ALL) in the European Union for a number of years in tablet form at a dose of 50 mg (date of licence: 19/07/1954 and date of validated Marketing Authorisation: 10/12/1997). No efficacy and safety study is available with the new mercaptopurine oral suspension formulation. The company has provided the results of a bioequivalence study comparing the oral suspension and the tablet form of mercaptopurine in healthy adult volunteers. It showed that the 50 mg XALUPRINE oral suspension, compared with the 50 mg tablet form of mercaptopurine:
- provides a higher area under the curve (AUC) of 13% which is reaching the limits of bioequivalence
- provides a higher maximum concentration (Cmax) of 39% (90% CI 22% to 58%) despite lower inter-individual variability (46% vs 69%) (coefficient of variation "CV" in %).

8.1 Efficacy

No study carried out with this galenic form of mercaptopurine.

8.2 Safety and adverse effects

No study carried out with this galenic form of mercaptopurine.

8.3 Summary & discussion

This application concerns a medicinal product where the active ingredient mercaptopurine has been used long-term in the curative treatment of acute lymphoblastic leukaemia (ALL) in tablet form only. For its application for inclusion on the list of medicines refundable by National Health Insurance, the company has provided the results of a bioavailability study, carried out on healthy adult volunteers, which concluded that there was a bioequivalence between the XALUPRINE 50 mg oral suspension and the 50 mg reference medicine in tablet form. No efficacy and safety study is available with this new galenic mercaptopurine formulation. Overall, this mercaptopurine oral suspension formulation, a medicinal product whose Marketing Authorisation goes back decades and one which has up to now only been available in tablet form, can now be used in a way that is specially adapted to the paediatric population.
9 THERAPEUTIC USE

Treatment of acute lymphoblastic leukaemia (ALL) occurs in three distinct phases: an induction phase, a consolidation phase and a maintenance phase.

The induction, the objective of which is to obtain remission, is achieved by combining several medicines, such as vincristine and prednisone (or dexamethasone) or daunorubicin and L-asparaginase (or PEG-L-asparaginase).

This phase requires additional treatment called consolidation, the objective of which is to eradicate in particular occult disease in the central nervous system (via the intrathecal administration of methotrexate because 6-mercaptopurine poorly penetrates the blood-brain barrier; Zimm 1985). Consolidation involves mercaptopurine, cyclophosphamide and cytarabine. Following these two steps, a maintenance treatment is undertaken; it combines daily mercaptopurine with weekly methotrexate, alternating it with medicines used during the induction treatment.

Mercaptopurine oral suspension treatment mainly falls within the scope of maintenance treatment of ALL in the paediatric population.
10 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee’s opinion is as follows:

10.1 Actual benefit

- Acute lymphoblastic leukaemia (ALL) is a serious, life threatening disease.
- This medicinal product is a specific, curative therapy for ALL.
- The efficacy/adverse effects ratio for XALUPRINE is high.
- This is a first-line therapy.
- There is a treatment alternative to XALUPRINE represented by the galenic tablet form of mercaptopurine, a form less suitable for children.

Public health benefit:
Acute lymphoblastic leukaemia (ALL) is a serious, life threatening but also rare disease (orphan disease). Its burden can be estimated to be low.
Treatment of rare diseases is a public health need, falling within the scope of the "Rare Diseases Plan 2010 – 2014" just like the development of medicines adapted for children (see report of the Committee to the European Parliament and the Council: “Better medicines for children - From concept to reality” of 24/6/2013).
In light of the available data (bioavailability alone), the additional impact of XALUPRINE on the morbidity and mortality and the quality of life of treated patients cannot be quantified. In the absence of data, the potential impact of XALUPRINE on the organisation of treatment (galenic form not requiring any changes for paediatric use) cannot be quantified.
The transferability of the results to current practice cannot be guaranteed, particularly because of the population included in the bioavailability trial (healthy adult volunteers).
XALUPRINE, because of its galenic form adapted to the paediatric population, provides a partial response to the public health need identified.
Overall, XALUPRINE presents a public health benefit in the treatment of acute lymphoblastic leukaemia in children. This benefit is low.

Taking account of these points, the Committee considers that the actual benefit of XALUPRINE is substantial in the indication and at the dosages in the Marketing Authorisation.

10.2 Improvement in actual benefit (IAB)

The mercaptopurine (XALUPRINE) oral suspension formulation, a medicinal product whose Marketing Authorisation goes back decades and one which has up to now only been available in tablet form, can now be used in a way that is specially adapted to the paediatric population. Because of this, the Committee considers that XALUPRINE provides a minor improvement in actual benefit (IAB IV) compared with mercaptopurine in tablet form in the paediatric population.
In adults and adolescents, XALUPRINE does not provide any improvement in actual benefit compared with mercaptopurine in tablet form (IAB V, non-existent).
10.3 Target population

The target population of XALUPRINE is mainly represented by children suffering from acute lymphoblastic leukaemia (ALL). The therapeutic need in adults and adolescents has been met by the tablet form, available for several decades. The French National Registries of Childhood Cancers in France 2000-2004 reports a total of 3,446 blood cancers, and on the other hand 29% of 8,473 of all childhood cancers (i.e. 2,457) are made up of forms of leukaemia (Lacour 2010). Among these patients, there have been about 450-470 new cases a year in France in children under 15 years of age (French National Registry of Childhood Haematopoietic Malignancies; Lacour 2010. French National Registry of Childhood Haematopoietic Malignancies; Goubin A and Clavel J 2004, Installations nucléaires de base et leucémies de l’enfant; Rapport du groupe de travail pluraliste 2011).

Taking into account both a survival rate of 5 years for acute forms of leukaemia estimated to be 85% in 1997-2000 (Goubin A and Clavel J. 2004) and the duration of mercaptopurine maintenance treatment of 2 to 3 years, the maximum number of patients (children) treated by XALUPRINE is estimated to be 1,500 patients (prevalent population).

The target population of XALUPRINE is estimated to be 1,500 patients at most.

11 TRANSPARENCY COMMITTEE RECOMMENDATIONS

The Committee recommends inclusion of XALUPRINE on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use in the indication and at the dosage in the Marketing Authorisation.

- Packaging: Appropriate for the prescription conditions.
- Proposed reimbursement rate: 100%