The legally binding text is the original French version

TRANSPARENCY COMMITTEE
Opinion
22 January 2014

EXJADE 125 mg, dispersible tablets

B/28 (CIP 34009 376 951 1 4)

B/84 (CIP 34009 376 952 8 2)

EXJADE 250 mg, dispersible tablets

B/28 (CIP 34009 376 953 4 3)

B/84 (CIP 34009 376 954 0 4)

EXJADE 500 mg, dispersible tablets

B/28 (CIP 34009 376 955 7 2)

B/84 (CIP 34009 376 956 3 3)

Applicant: NOVARTIS PHARMA SAS

INN	deferasirox
ATC Code (2012)	V03AC03 (iron chelating agent)
Reason for the review	Extension of indication
Lists concerned	National Health Insurance (French Social Security Code L.162-17) Hospital use (French Public Health Code L.5123-2)
Indication concerned	"EXJADE is also indicated for the treatment of chronic iron overload requiring chelation therapy when deferoxamine therapy is contraindicated or inadequate in patients with non-transfusion dependent thalassaemia syndromes aged 10 years and older "

Actual Benefit	The actual benefit of EXJADE in the treatment of iron overload in patients with non-transfusion-dependent thalassaemia is substantial.
Improvement in Actual Benefit	<p>In the treatment of chronic iron overload requiring chelation therapy when deferoxamine therapy is contraindicated or inadequate in patients with non-transfusion-dependent thalassaemia syndromes aged 10 years and older, given:</p> <ul style="list-style-type: none"> - the procedures for demonstrating the efficacy of EXJADE in the pivotal study, whose results must be interpreted with caution, - the lack of alternative therapies in patients who cannot take deferoxamine, - uncertainties with regard to long-term renal safety, which may prove to be of particular concern in paediatrics, - the lack of available data on the possibility of retreatment in patients who reaccumulate iron after having achieved a satisfactory body iron level, - the difficulty of identifying the population for whom deferoxamine therapy is inadequate and therefore the associated risk of misuse, <p>the Committee believes that the improvement in actual benefit of EXJADE is minor (level IV)</p>
Therapeutic use
Recommendations

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	Initial date (centralised rapporteur state: France): 28/08/2006 Date of extension of indication: 20/12/2012 The Marketing Authorisation is associated with a risk management plan and a request for an additional study (an observational cohort study in patients age 10 or older with non-transfusion-dependent thalassaemia).
Prescribing and dispensing conditions/special status	List I Orphan medicinal product Medicine for initial six-monthly hospital prescription. Medicine requiring special monitoring during treatment.
ATC Classification	2012; V V03 V03A V03AC V03AC03 Various All other therapeutic products All other therapeutic products Iron chelating agents deferasirox

02 BACKGROUND

This is an application for listing EXJADE in a new indication "treatment of chronic iron overload requiring chelation therapy when deferoxamine therapy is contraindicated or inadequate in patients with non-transfusion-dependent thalassaemia syndromes aged 10 years and older".

EXJADE was already indicated in the treatment of chronic iron overload caused by:

- frequent blood transfusions (≥ 7 ml/kg/month of packed red blood cells) in patients age 6 or older and who have betathalassaemia major.
- blood transfusions when deferoxamine treatment is contraindicated or inadequate in certain groups of patients.

These indications were examined by the Transparency Committee on 20/09/2006.

An opinion for renewal of inclusion for all the indications of this proprietary medicinal product will be delivered at the same time and be the subject of a specific opinion.

03 THERAPEUTIC INDICATIONS

"EXJADE is indicated for the treatment of chronic iron overload requiring chelation therapy when deferoxamine therapy is contraindicated or inadequate in patients with non-transfusion dependent thalassaemia syndromes aged 10 years and older.

EXJADE is indicated for the treatment of chronic iron overload due to frequent blood transfusions (≥ 7 ml/kg/month of packed red blood cells) in patients with beta thalassaemia major aged 6 years and older.

EXJADE is also indicated for the treatment of chronic iron overload due to blood transfusions when deferoxamine therapy is contraindicated or inadequate in the following patient groups:

- in patients with beta thalassaemia major with iron overload due to frequent blood transfusions (≥ 7 ml/kg/month of packed red blood cells) aged 2 to 5 years,
- in patients with beta thalassaemia major with iron overload due to infrequent blood transfusions (< 7 ml/kg/month of packed red blood cells) aged 2 years and older,

- in patients with other anaemias aged 2 years and older. "

04 DOSAGE

"Chelation therapy should only be initiated when there is evidence of iron overload (liver iron concentration [LIC] ≥ 5 mg Fe/g dry weight [dw] or serum ferritin consistently >800 $\mu\text{g/l}$). LIC is the preferred method of iron overload determination and should be used wherever available. Caution should be taken during chelation therapy to minimise the risk of over-chelation in all patients.

Starting dose: The recommended initial daily dose of EXJADE in patients with non-transfusion-dependent thalassaemia syndromes is 10 mg/kg body weight.

Dose adjustment It is recommended that serum ferritin be monitored every month. After every 3 to 6 months of treatment, a dose increase in increments of 5 to 10 mg/kg should be considered if the patient's LIC is ≥ 7 mg Fe/g dw, or if serum ferritin is consistently >2000 $\mu\text{g/l}$ and not showing a downward trend, and the patient is tolerating the medicinal product well. Doses above 20 mg/kg are not recommended because there is no experience with doses above this level in patients with non transfusion-dependent thalassaemia syndromes.

In patients in whom LIC was not assessed and serum ferritin is ≤ 2000 $\mu\text{g/l}$, dosing should not exceed 10 mg/kg.

For patients in whom the dose was increased to >10 mg/kg, dose reduction to 10 mg/kg or less is recommended when LIC is $7 < \text{mg Fe/g dw}$ or serum ferritin is ≤ 2000 $\mu\text{g/l}$.

Treatment cessation Once a satisfactory body iron level has been achieved (LIC < 3 mg Fe/g dw or serum ferritin < 300 $\mu\text{g/l}$), treatment should be stopped. **There are no data available on the retreatment of patients who reaccumulate iron after having achieved a satisfactory body iron level and therefore retreatment cannot be recommended.** "

For special populations, refer to the SPC.

05 THERAPEUTIC NEED^{1, 2}

Thalassaemias are hereditary diseases characterised by a reduction in the normal production of haemoglobin (Hb) due to a synthesis defect in the alpha-globin chain (alpha thalassaemia) or the betaglobin chains (beta thalassaemia).

Three main types of beta thalassaemia (BT) are described (BT minor, intermediate and major) and likewise for alpha thalassaemia (alpha plus thalassaemia and alpha thalassaemia trait, haemoglobin H and Bart's hydrops fetalis).

Thalassaemia intermediate (TI) is defined clinically with a less severe anaemia and later discovery than in thalassaemia major. The criterion applied in the national TI group registry is: no indication for a systematic transfusion regimen before age 4 (a systematic transfusion regimen is defined by eight or more transfusions per year). Cases of TI are variable in their clinical presentation, with very varied degrees of anaemia.

Therefore, only the less severe forms of thalassaemia are non-transfusion-dependent (NTDT); these are:

- beta thalassaemia intermediate (BTI),
- some types of haemoglobin E - beta thalassaemia (HBe-BT, and some types of haemoglobin H (alphathalassaemia).

In these patients, the overload is of gradual onset and becomes detectable only after age 10; its extent is not the consequence of transfusions but of an exaggerated absorption of iron in the gut and a poor internal iron circuit due to ineffective erythropoiesis. Untreated, after age 30, the iron overload becomes comparable to patients with thalassaemia major on a chronic transfusion programme.

These iron overloads are treated by prescribing iron chelators; DESFERAL (deferroxamine) is the first-line treatment, administered parenterally and available in both community and hospital pharmacies. This proprietary medicinal product may be administered by:

- slow subcutaneous route using a miniaturised portable infusion pump over a period of 8 to 12 hours, or even 24 hours, to be used 5 to 7 times per week.
- intravenous infusion during a blood transfusion,
- continuous intravenous infusion: implantable systems may be used for an intensive chelator treatment.

Given the cumbersome mode of administration of DESFERAL, which is restrictive for the patient, there is a therapeutic need for providing oral proprietary medicinal products.

¹ Syndromes thalassémiques majeurs et intermédiaires [Thalassaemia major and intermediate syndromes]. Guide ALD HAS[HAS Long Term Conditions Guide] June 2008.

² Orphanet.

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

There are other iron chelators available on the market.

NAME (INN) Company	Same TC* Yes/No	Indication	Date of opinion	AB/IAB (Wording)	Reimburse ment Yes/No
DESFERAL (deferioxamine) Novartis Pharma	Yes	Secondary haemosiderosis	23/03/ 2011	Substantial AB IAB N/A	Yes
FERRIPROX (deferiprone)	Yes	Treatment of iron overload in patients with thalassaemia major for whom deferioxamine treatment is contraindicated or inadequate	12/04/ 2000	Substantial AB IAB I relative to no treatment when deferioxamine is contraindicated or accompanied by severe toxicity in patients with thalassaemia major	Yes

*therapeutic category

06.2 Other health technologies

Not applicable

► Conclusion

In the extension of indication "treatment of chronic iron overload requiring chelation therapy when deferioxamine therapy is contraindicated or inadequate in patients with non-transfusion-dependent thalassaemia syndromes aged 10 years and older" there is no relevant comparator.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

Country	REIMBURSEMENT
YES/NO If not, why not	Population(s) That of the Marketing Authorisation or restricted
Switzerland	In progress
Germany	In progress
Netherlands	In progress
Greece	In progress
Sweden	In progress
United Kingdom	In progress

08 SUMMARY OF PREVIOUS ASSESSMENTS

Date of opinion (reason for request)	20/09/2006 Inclusion
Indication	<p>Treatment of chronic iron overload due to frequent blood transfusions (≥ 7 ml/kg/month of packed red blood cells) in patients with beta thalassaemia major aged 6 years and older (indication 1).</p> <p>Treatment of chronic iron overload due to blood transfusions when deferoxamine therapy is contraindicated or inadequate in the following patient groups:</p> <ul style="list-style-type: none"> - patients with other anaemias, - patients aged 2 to 5 years, - patients with beta thalassaemia major with iron overload due to infrequent blood transfusions (< 7 ml/kg/month of packed red blood cells), (indication 2)
AB (wording)	Substantial
IAB (wording)	<p>Indication 1: <i>The Transparency Committee, despite the failure to strictly demonstrate the non-inferiority of EXJADE relative to DESFERAL in the overall population of study 107 and the risks of renal intolerance, considers that EXJADE provides a moderate improvement in actual benefit (level III) relative to DESFERAL given the improvement in quality of life that it brings about and procedures for use that permit better patient management.</i></p> <p>Indication 2: <i>In this second indication, the Transparency Committee considers that EXJADE provides a substantial improvement in actual benefit (level II) when no other treatment can be offered. In the situation where FERRIPROX can be used, the Transparency Committee cannot rule on the respective performances of these two medicinal products due to lack of comparative data.</i></p>
Studies Requested	<p>"The Transparency Committee would like a follow-up study to be conducted on patients treated with EXJADE".</p> <p>The results of this study shall be presented in the renewal of inclusion opinion.</p>

09 ANALYSIS OF AVAILABLE DATA

The request for extension of indication relies on:

- A phase II clinical study (Thalassa Study - A2209) whose objective was to compare the efficacy of EXJADE relative to placebo in terms of reducing liver iron concentration (LIC) in patients with NTDT.
- A phase I/II open-label study (A2202) which evaluated the safety of EXJADE in patients with hereditary haemochromatosis,
- Two publications (Ladis 2010 and Voskaridou 2010) which evaluated the safety of EXJADE. Given their methodology (small number of subjects (n=11), open label nature, etc.), these studies will not be discussed in detail in this opinion.

09.1 Efficacy

Thalassa Study (A2209)

Method: EXJADE (5 and 10 mg) phase II comparative, placebo-controlled, randomised, double blind study evaluating efficacy in terms of reducing LIC at 52 weeks in 166 patients with non-transfusion-dependent thalassaemia (NTDT).

Inclusion criteria: Patients age 10 and older with NTDT:

- who have not received a transfusion for 6 months,
- with an LIC ≥ 5 mg Fe/g measured by R2 NMR and serum ferritin >300 ng/ml.

Treatments:

EXJADE 5 mg, n=55

EXJADE 10 mg, n=55,

Placebo, n=56.

Primary efficacy endpoint: Change in liver iron concentration at 52 weeks compared to baseline.

RESULTS:

At baseline, the patients' characteristics were not strictly comparable. Differences are observed in terms of:

- Baseline LIC (whose levels have an impact on the potential efficacy of the treatments): patients of the EXJADE group had higher levels than those of the placebo group with an LIC >7 mg Fe/g dw in 81.9% of patients of the EXJADE 5 mg group, 85.5% of patients of the EXJADE 10 mg group and 75% of patients of the placebo group.
- Transfusion history (which has an impact on iron overload): 89.1%, 90.9% and 82.1% of patients.
- Prior treatments with iron chelators (which provides information on patient profile and especially on treatment resistance): 14.5%, 29.1% and 35.7% of patients.

The characteristics of patients at baseline, which are not strictly comparable especially in terms of LIC, history of transfusions and chelator treatment, may possibly overestimate the effect observed.

Hbe-thalassaemia was diagnosed in 29.5% of patients, while 57.2% of patients had beta thalassaemia (severity not specified) and 13.3% had alpha thalassaemia (severity not specified). Thus, whether or not the thalassaemia of the patients included was transfusion-dependent (as defined in the extension of indication) could not be specified given the available information.

After 52 weeks of treatment, a significant reduction of LIC was observed in both groups treated with EXJADE relative to placebo:

- With EXJADE 5 mg, reduction of -1.95 mg/Fe/g dw $[-2.84; -0.96]$ versus 0.38 $[-0.59; 1.34]$ on placebo, difference -2.33 $[-3.89; -0.76]$, $p < 0.001$.

- With EXJADE 10 mg, reduction of -3.80 mg/Fe/g dw [-4.76; -2.85] versus 0.38 [-0.59; 1.34] on placebo, difference -4.18 [-5.71; -2.64], p<0.001.

Given the characteristics of patients at baseline, which are not strictly comparable especially in terms of LIC, history of transfusions and chelator treatment, the results of this Thalassa study must be interpreted with caution.

09.2 Adverse effects

9.2.1. From studies

In the Thalassa study, adverse effects were observed in 13/55 patients (23.6%) of the EXJADE 5 mg group, 18/55 patients (32.7%) of the EXJADE 10 mg group and 9/56 patients (16.1%) of the placebo group. The most common adverse effects (>10%) were:

- Diarrhoea: 0 patients versus 5 patients versus 1 patients,
- Rash: 2 versus 5 versus 1,
- Nausea: 3 versus 4 versus 4,

In study A2202, conducted in patients with hereditary haemochromatosis, adverse effects were observed in 35/49 patients (71.4%): The most common adverse effects (> 10%) were:

- Gastrointestinal disorders (diarrhoea, nausea, abdominal pain): 49%
- Disturbances in laboratory parameters (creatinine, ALAT): 28.6%

These adverse effects were more common in the EXJADE 10 mg than in the EXJADE 5 mg group.

9.2.2. From the SPC

According to the SPC, the most commonly reported adverse effects during chronic treatment with EXJADE in adult and paediatric patients include gastrointestinal disorders in around 26% of patients (mainly nausea, vomiting, diarrhoea or abdominal pain) and a skin rash in around 7% of patients. These reactions are dose dependent, basically mild to moderate, generally transient and for the most part resolve even if treatment is continued.

During clinical trials, increases of more than 33% of serum creatinine, sometimes above the upper normal limit and obtained on at least two successive occasions, were observed in 36% of patients. They were dose dependent.

The safety profile for EXJADE is no different from one indication to the other.

9.2.3. Pharmacovigilance and RMP data

The main adverse effect of EXJADE identified in the RMP is creatinine elevation. The other risks identified in the RMP are tubulopathies, elevated transaminases, gastrointestinal bleeding, ulcers and oesophagitis, hearing loss and eye disorders. For more information on these risks and their monitoring, refer to the EMA website³.

Opinion of the Pharmacovigilance Technical Committee of 19/09/2013⁴

Discussion

"The discussions of the Pharmacovigilance Technical Committee members essentially related to optic neuritis, acute tubular necrosis, nephrolithiasis, hypocalcaemia, hyperammonaemia, DRESS, agranulocytosis/febrile neutropenia and death.

Given the data presented, it appears necessary to add the following adverse effects to EXJADE's SPC. "GI perforations", "acute tubular necrosis", "nephrolithiasis", "optic neuritis" (especially as this adverse effect is one of the risks identified in the European RMP) and "neutropenia."

³http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000670/WC500138928.pdf.

⁴<http://ansm.sante.fr/Mediatheque/Publications/Ordres-du-jour-comptes-rendus-des-groupes-de-travail-comites-commissions-Comites-techniques>.

A detailed review of cases of death (relative to doses administered), DRESS (with broadened search criteria) and hypocalcaemia and enhanced monitoring of cases of osteomalacia and hyperammonaemia should be done in the next PSURS. The question of the selectivity of deferasirox for calcium and the need to monitor serum calcium in the patients treated (especially in paediatrics) is posed. The affinity of deferasirox for divalent cations, especially calcium, must be specified given that these data appear in the SPC for DESFERAL.

Moreover, paediatric patients must be especially monitored (in particular, since obtaining the new indication in patients above age 10 with non-transfusion-dependent thalassaemia syndrome). Monitoring of renal effects, especially in paediatrics, is even more important since treatment may be long term in these patients.

Conclusions of the Pharmacovigilance Technical Committee (PVTC)

"The members of the Pharmacovigilance Technical Committee are unanimously in favour of maintaining national monitoring of all the adverse effects of EXJADE.

The company will be asked to provide precise exposure data for paediatric patients.

Moreover, all the available data concerning off-label use, including situations that could potentiate the occurrence of adverse effects (use in contraindicated situations, use in patients with low serum ferritin) must be submitted.

The following adverse effects: "GI perforations", "acute tubular necrosis", "nephrolithiasis", "optic neuritis" and "neutropenia" should be added to the "undesirable effects" section of the EXJADE SPC.

A detailed review of cases of death, DRESS and hypocalcaemia and enhanced monitoring of cases of osteomalacia and hyperammonaemia will be required from the company as part of the next PSUR.

The opinion of the "Drug Interactions" (DI) working group will be requested regarding interactions between deferasirox and lithium, on the one hand, and deferasirox and busulfan on the other hand. "

Therefore, continued monitoring has been considered vital by the PVTC due to the sustained rates of reporting for some time after Marketing Authorisation, the major role of serious adverse effects, the use in paediatrics and the toxicities described. The recommendations of the PVTC are being assessed by the EMA.

09.3 Summary & discussion

Primary efficacy data:

The request for extension of indication primarily relies on the phase II clinical study Thalassa (A2209) whose objective was to compare the efficacy of EXJADE relative to placebo in terms of reducing liver iron concentration (LIC) in 166 patients with NTDT.

After 52 weeks of treatment, a significant reduction of LIC was observed in both groups treated with EXJADE relative to placebo:

- With EXJADE 5 mg, reduction of -1.95 mg/Fe/g dw [-2.84; -0.96] versus 0.38 [-0.59; 1.34] on placebo, difference -2.33 [-3.89; -0.76], $p < 0.001$.
- With EXJADE 10 mg, reduction of -3.80 mg/Fe/g dw [-4.76; -2.85] versus 0.38 [-0.59; 1.34] on placebo, difference -4.18 [-5.71; -2.64], $p < 0.001$.

These results must be interpreted with consideration that the observed effect may be overestimated due to patient characteristics at baseline that are not strictly comparable, especially in terms of LIC, history of transfusion and chelator treatment.

Primary safety data:

The main adverse effect of EXJADE identified in the RMP is serum creatinine elevation. The other most common adverse effects are gastrointestinal disorders in around 26% of patients (mainly nausea, vomiting, diarrhoea or abdominal pain) and skin rash in around 7% of patients.

Following analysis of the latest PSURs, the members of the Pharmacovigilance Technical Committee were unanimously in favour of maintaining national monitoring of all the adverse effects of EXJADE.

Moreover, the PVTC recommended that the following adverse effects: "GI perforations", "acute tubular necrosis", "nephrolithiasis", "optic neuritis", and "neutropenia" should be added to the "undesirable effects" section of the EXJADE SPC.

A detailed review of cases of death, DRESS and hypocalcaemia and enhanced monitoring of cases of osteomalacia and hyperammonaemia will be required from the company as part of the next PSUR.

Moreover, paediatric patients must be especially monitored (in particular, since obtaining the new indication in patients above age 10 with non-transfusion-dependent thalassaemia syndrome). Monitoring of renal effects, especially in paediatrics is even more important since treatment may be long term in these patients.

Therefore, continued monitoring has been considered vital by the PVTC due to the sustained rates of reporting for some time after Marketing Authorisation, the major role of serious adverse effects, the use in paediatrics and the toxicities described.

Discussion:

Given the characteristics of patients at baseline, which are not strictly comparable, especially in terms of LIC, history of transfusions and chelator treatment, the results of this Thalassa study must be interpreted with the consideration that the observed effect may be overestimated.

Moreover, there are no specific data available in the indication of the Marketing Authorisation, i.e., patients in whom treatment with deferoxamine is contraindicated or inadequate.

In terms of safety, a sustained rate of adverse effects reported for some time after the Marketing Authorisation was observed in the latest PSURs with a significant share of serious adverse effects and uncertainties regarding long-term renal safety, which may prove to be of particular concern in paediatrics.

There are currently no data available on the retreatment of patients who reaccumulate iron after having achieved a satisfactory body iron level.

09.4 Planned studies

The Marketing Authorisation is associated with a risk management plan and a request for an observational cohort study in patients age 10 or older with non-transfusion-dependent thalassaemia.

010 THERAPEUTIC USE

Thalassaemia disorders are hereditary diseases characterised by a reduction in the normal production of haemoglobin (Hb) due to a synthesis defect in the alpha-globin chain (alpha thalassaemia) or the beta-globin chains (betathalassaemia).

Only the less severe forms of thalassaemia are non transfusion dependent (NTDT); these are:

- beta thalassaemia intermediate (BTI),
- some types of haemoglobin-E beta thalassaemia (HBe-BT) and some types of haemoglobin H (alpha thalassaemia) where the anaemia is less severe and may or may not require occasional transfusions.

Patients with NTDT have ineffective erythropoiesis, leading to an increase in growth and differentiation factor 15 (GDF15). In this context, an overload of iron may develop in adults even in the absence of blood transfusions, however, less frequently than in severe forms of thalassaemia.

These iron overloads are managed by prescribing iron chelators; DESFERAL (deferroxamine) is the first-line treatment, administered by injection and available in both community and hospital pharmacies.

Role of EXJADE:

Given its indication, EXJADE (deferasirox) can be offered to patients when treatment with deferroxamine is contraindicated or inadequate. However, the Committee would like to point out that the term "inadequate" is imprecise and opens the possibility of misuse of EXJADE as a first-line treatment in all patients.

011 TRANSPARENCY COMMITTEE CONCLUSIONS

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

011.1 Actual Benefit

- ▮ Iron overload may be complicated by disorders with serious consequences in terms of morbidity and mortality and can be life threatening.
- ▮ This medicinal product, an iron chelator, may be considered a curative treatment.
- ▮ Its efficacy/adverse effects ratio is high.
- ▮ There are treatment alternatives for the majority of patients.
- ▮ Second-line treatment in patients in whom deferoxamine is poorly tolerated or inadequate.

▮ Public health benefit:

Iron overload is a serious complication but it appears infrequently in non-transfusion-dependent thalassaemia, corresponding to the least severe forms of the disease. Therefore, the burden represented by the extension of indication for EXJADE is at best low, due to the rarity of the diseases concerned (BTI, some types of HBe-BT and haemoglobin H) and the fact that this treatment is limited to patients in whom treatment with deferoxamine is contraindicated.

Since improving the management of rare diseases is an identified priority (GTNDO [National Technical Group for Definition of Public Health Objectives]*, Rare Disease Plan), the treatment of these conditions is a public health need.

In view of the available data, in the absence of data versus active comparator, the additional impact of EXJADE on morbidity and mortality and quality of life of patients treated is not quantifiable. No impact on the organisation of healthcare is expected.

The transposability of results is not guaranteed, especially due to a difference at baseline from the placebo group (in terms of LIC, transfusion history and prior iron chelator treatments) that could have led to an overestimation of the effect of EXJADE, the inclusion of patients for whom it was not determined whether or not their disease was transfusion-dependent and due to the absence of data for patients fitting the extension of indication (those for whom treatment with deferoxamine is contraindicated or inadequate).

In all, it is not expected that EXJADE will benefit public health in this extension of indication.

Taking account of these points, the Committee finds that actual benefit of EXJADE is substantial in the extension of indication "treatment of chronic iron overload requiring chelation therapy when deferoxamine therapy is contraindicated or inadequate in patients with non-transfusion-dependent thalassaemia syndromes aged 10 years and older".

The Committee recommends inclusion on the list of medicines refundable by National Health Insurance and/or on the list of medicines approved for hospital use in the extension of indication "treatment of chronic iron overload requiring chelation therapy when deferoxamine therapy is contraindicated or inadequate in patients with non-transfusion-dependent thalassaemia syndromes aged 10 years and older" and at the dosages in the Marketing Authorisation.

▮ **Proposed reimbursement rate: 65%**

011.2 Improvement in actual benefit (IAB)

In the treatment of chronic iron overload requiring chelation therapy when deferoxamine therapy is contraindicated or inadequate in patients with non-transfusion-dependent thalassaemia syndromes aged 10 years and older, given:

- the procedures for demonstrating the efficacy of EXJADE in the pivotal study, whose results must be interpreted with caution,
- the lack of alternative therapies in patients who cannot take deferoxamine,
- the uncertainties with regard to long-term renal safety, which may prove to be of especial concern in paediatrics,
- the lack of available data on the possibility of retreatment in patients who reaccumulate iron after having achieved a satisfactory body iron level,
- the difficulty of identifying the population for whom deferoxamine therapy is inadequate and therefore the associated risk of misuse,

the Committee believes that the improvement in actual benefit of EXJADE is minor (level IV)

011.3 Target population

The target population for EXJADE in this extension of indication is patients age 10 or older with non-transfusion dependent thalassaemia syndromes when treatment with deferoxamine is contraindicated or inadequate. This population can be estimated from the following data:

Only the least severe forms of thalassaemia are non transfusion dependent (NTDT); these are:

- beta thalassaemia intermediate (BTI),
- some types of haemoglobin E - beta thalassaemia (HBe-BT) and some types of haemoglobin H (alpha thalassaemia) where the anaemia is less severe and may or may not require occasional transfusions.

According to the national registry of thalassaemia patients:

- 163 patients have a diagnosis of beta thalassaemia intermediate, including 80% that are not transfusion-dependent,
- 80 patients had diagnosis of alpha thalassaemia intermediate, are in general less anaemic than beta thalassaemia patients and remain mostly transfusion-independent.

Given the available data, the target population for EXJADE in this extension of indication may be estimated to be at most 200 patients.

012 COMMITTEE RECOMMENDATIONS

► Packaging

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