Regulatory Affairs, Global Drug Development

Novartis Pharma Services Inc.,
Representative Office Malta,
79, Simpson Str., Marsa, MRS 1000

Tel: +356 22487241
Fax: +356 22487249

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Exjade® film-coated tablets (deferasirox): new formulation, new posology, and new method of administration: risk of medication error

Dear Healthcare Professional,

Novartis, in association with the European Medicines Agency and Malta Medicines Authority, would like to inform you of a new film-coated tablet formulation of deferasirox:

Exjade® film-coated tablets (deferasirox) 90 mg, 180 mg, and 360 mg

The current formulation of deferasirox, Exjade dispersible tablets, and the new formulation, Exjade film-coated tablets, have the same active ingredient, and the same indications (see Therapeutic Indications section below). In order to minimize the risk of medication error due to prescriptions written by generic name that do not specify either the formulation or the strength, Novartis reminds you of the relevant differences between the film-coated tablet and dispersible tablet:

Summary

Exjade film-coated tablets – important information:

- Dosed and administered differently from Exjade dispersible tablets – Exjade film- coated tablets are a strength-adjusted formulation of deferasirox, with higher bioavailability compared to Exjade dispersible tablets
- Available in three strengths: 90 mg, 180 mg, and 360 mg
- The dose range is 7 to 28 mg/kg of patient body weight; dose modifications for safety or efficacy should be in steps of 3.5 or 7 mg/kg
- The two formulations are differentiated by tablet form, color, size and packaging

Switching from Exjade dispersible tablets to Exjade film-coated tablets:

- When switching from one formulation to another, a dose conversion must be calculated (please see below dose conversion table)

To avoid dosing errors, it is important that the prescription specifies the type of formulation (dispersible tablet or film-coated tablet), the prescribed dose in mg/kg/day, <u>and</u> the calculated total dose per day with strength of film-coated or dispersible tablets.

Further information

- A new posology and new method of administration must be applied when switching patients between dispersible tablets and film-coated tablets of deferasirox. Exjade film-coated tablets are a strength-adjusted formulation of deferasirox with higher bioavailability compared to dispersible tablets

Important differences between the dispersible tablets and the film-coated tablets

	CURRENT FORMULATION	NEW FORMULATION
	EXJADE DISPERSIBLE TABLETS	**EXJADE FILM-COATED TABLETS**
Strengths	125 mg, 250 mg, 500 mg	90 mg, 180 mg, 360 mg
Packaging		
Description of tablets	Round, white tablets available in three strengths: 125 mg (white), 250 mg (white), 500 mg (white) (*Tablets shown are not actual size*) 	Ovaloid, biconvex available in three strengths: 90 mg (light blue), 180 mg (medium blue), and 360 mg (dark blue) (*Tablets shown are not actual size*) 
Administration	Dispersible tablets should be mixed in water, orange juice, or apple juice. Dispersible tablets must not be chewed or swallowed whole.	Film-coated tablets can be swallowed whole with some water. Film-coated tablets can be crushed and administered by sprinkling onto soft food such as yogurt or applesauce (pureed apple). The dose should be immediately and completely consumed, and not stored for future use.
	Must be taken on an empty stomach, at least 30 minutes before food	May be taken on an empty stomach or with a light meal
	Contains lactose	Does not contain lactose

Dose conversion between the dispersible tablets and the film-coated tablets
When converting the patient's prescription to Exjade film-coated tablets, the dose of the film-coated tablets should be 30% lower than the dose of dispersible tablets, rounded to the nearest whole tablet.

	CURRENT FORMULATION	**NEW FORMULUATION**
	EXJADE DISPERSIBLE TABLETS	**EXJADE FILM-COATED TABLETS**
Dose range	**10 to 40 mg/kg/day** Calculated and rounded to the nearest whole tablet size.	**7 to 28 mg/kg/day** Calculated and rounded to the nearest whole tablet size.
Recommended initial daily dose	20 mg/kg/day (TIO) 10 mg/kg/day (NTDT)	14 mg/kg/day (TIO) 7 mg/kg/day (NTDT)
Dose adjustment	Increments of 5-10 mg/kg	Increments of 3.5-7 mg/kg
Therapeutic dose range	Exjade dispersible tablets • 10 mg/kg/day • 20 mg/kg/day • 30 mg/kg/day • 40 mg/kg/day	Exjade film-coated tablets • 7 mg/kg/day • 14 mg/kg/day • 21 mg/kg/day • 28 mg/kg/day
Calculated dose example for 50 kg patient receiving	Exjade dispersible tablets TIO: 20 mg/kg/day: 20 mg/kg * 50 kg = 1000 mg/day Two (2) 500 mg tablets NTDT: 10 mg/kg/day: 10 mg/kg * 50 kg = 500 mg/day One (1) 500 mg tablet	Exjade film-coated tablets TIO: 14 mg/kg/day: 14 mg/kg * 50 kg = 700 mg/day Two (2) 360 mg/tablets NTDT: 7 mg/kg/day: 7 mg/kg * 50 kg = 350 mg/day One (1) 360 mg tablet

TIO, transfusional iron overload; NTDT, non-transfusion-dependent thalassaemia.

Please share this information with relevant colleagues and health care professionals.

Therapeutic indication

The new formulation is indicated for the same patient populations as the current formulation:

Exjade film-coated tablets are 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 film-coated tablets also are 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 paediatric 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 adult and paediatric 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 adult and paediatric patients with other anaemias aged 2 years and older

Exjade film-coated tablets also are 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.

Please refer to the Summary of Product Characteristics (SmPC) for a complete description of the product.

Call for reporting

1. As per the SmPC black triangle, doctors are prompted to report serious ADRs and certain selected ADRs

This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse drug reactions.

Reporting suspected adverse drug reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected or unsuspected adverse drug reactions associated with these products in accordance with the national spontaneous reporting system. Report forms can be downloaded from www.medicinesauthority.gov.mt/adrportal and posted to Medicines Autority Post-Licensing Directorate Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SGN 3000 or sent by email to postlicensing.medicinesauthority@gov.mt

Healthcare professionals may also report any adverse events suspected to be associated with the use of Exjade to *Novartis Pharma Services Inc. Representative Office Malta by phone on +35621222872, by fax on +35622487219 or e-mail at drug_safety.malta@novartis.com*

Company contact point

If you have any further questions or require additional information please contact *Novartis Pharma Services Inc., Representative Office Malta, by phone on +35621222872, by fax on +35622487219 or e-mail at novartis.malta@novartis.com*

Annexes

1. Additional letter regarding planned discontinuation of Exjade dispersible tablets in the market dated 25-01-2017
2. Local label and Package Insert

Kind regards,

Jacqueline Scerri
Medical Head

c/o Graziella Vella
RA Head

25/01/2017

Annex 1

25-01-2017

Discontinuation of Exjade® (deferasirox) dispersible tablets

Dear Healthcare Professional,

Novartis would like to inform you that Exjade® dispersible tablets will no longer be available in Malta in the near future because a new Exjade film-coated tablet formulation of deferasirox is now available.

In agreement with the European Medicines Agency and the Malta Medicines Authority, Novartis is planning to stop shipments of Exjade (deferasirox) dispersible tablets to Malta by 04-17 as an important risk mitigation measure, to minimize medication errors in the interest of patient safety.

Summary

- Exjade film-coated tablets, a new oral formulation of deferasirox that can be swallowed whole or crushed onto soft food, is now available, with the same active ingredient as Exjade dispersible tablets, and will replace Exjade dispersible tablets on the market in Malta
- Exajde film-coated tablets are a strength-adjusted formulation of deferasirox with higher bioavailability than the dispersible tablets, rounded to the nearest whole film-coated tablet
- Exjade dispersible tablets shipment will be discontinued as of 04-17

Please see the separate letter (attached) [dated DD-01-17] providing full details on the introduction of the new film-coated tablets

Further information

- This commercial discontinuation of the deferasirox formulation as the dispersible tablet is not a recall and is not due to any concerns of any nature with the dispersible tablets

Adverse event reporting

Healthcare professionals are asked to report any suspected adverse drug reactions. Reporting suspected adverse drug reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected or unsuspected adverse drug reactions associated with these products in accordance with the national spontaneous reporting system. Report forms can be downloaded from www.medicinesauthority.gov.mt/adrportal and posted to Medicines Autority Post-Licensing Directorate Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann or sent by email to postlicensing.medicinesauthority@gov.mt

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Annex 2

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

EXJADE 90 mg film-coated tablets
EXJADE 180 mg film-coated tablets
EXJADE 360 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

EXJADE 90 mg film-coated tablets
Each film-coated tablet contains 90 mg deferasirox.

EXJADE 180 mg film-coated tablets
Each film-coated tablet contains 180 mg deferasirox.

EXJADE 360 mg film-coated tablets
Each film-coated tablet contains 360 mg deferasirox.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

EXJADE 90 mg film-coated tablets
Light blue, ovaloid, biconvex film-coated tablet with bevelled edges and imprints (NVR on one face and 90 on the other). Approximate tablet dimensions 10.7 mm x 4.2 mm.

EXJADE 180 mg film-coated tablets
Medium blue, ovaloid, biconvex film-coated tablet with bevelled edges and imprints (NVR on one face and 180 on the other). Approximate tablet dimensions 14 mm x 5.5 mm.

EXJADE 360 mg film-coated tablets
Dark blue, ovaloid, biconvex film-coated tablet with bevelled edges and imprints (NVR on one face and 360 on the other). Approximate tablet dimensions 17 mm x 6.7 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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 paediatric 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 adult and paediatric 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 adult and paediatric patients with other anaemias aged 2 years and older.

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.

4.2 Posology and method of administration

Treatment with EXJADE should be initiated and maintained by physicians experienced in the treatment of chronic iron overload.

Posology

Transfusional iron overload

It is recommended that treatment be started after the transfusion of approximately 20 units (about 100 ml/kg) of packed red blood cells (PRBC) or when there is evidence from clinical monitoring that chronic iron overload is present (e.g. serum ferritin >1,000 µg/l). Doses (in mg/kg) must be calculated and rounded to the nearest whole tablet size.

The goals of iron chelation therapy are to remove the amount of iron administered in transfusions and, as required, to reduce the existing iron burden.

EXJADE film-coated tablets demonstrate higher bioavailability compared to the EXJADE dispersible tablet formulation (see section 5.2). In case of switching from dispersible tablets to film-coated tablets, the dose of the film-coated tablets should be 30% lower than the dose of the dispersible tablets, rounded to the nearest whole tablet.

The corresponding doses for both formulations are shown in the table below.

Table 1 Recommended doses for transfusional iron overload

	Film-coated tablets	Dispersible tablets	Transfusions	Serum ferritin
Starting dose	**14 mg/kg/day**	**20 mg/kg/day**	After 20 units (about 100 ml/kg) of PRBC	OR >1,000 µg/l
Alternative starting doses	21 mg/kg/day	30 mg/kg/day	>14 ml/kg/month of PRBC (approx. >4 units/month for an adult)	
	7 mg/kg/day	10 mg/kg/day	<7 ml/kg/month of PRBC (approx. <2 units/month for an adult)	
For patients well managed on deferoxamine	One third of deferoxamine dose	Half of deferoxamine dose		
Monitoring				**Monthly**
Target range				**500-1,000 µg/l**
Adjustment steps (every 3-6 months)	**Increase**			>2,500 µg/l
	3.5 - 7 mg/kg/day Up to 28 mg/kg/day	5-10 mg/kg/day Up to 40 mg/kg/day		
	Decrease			
	3.5 - 7 mg/kg/day In patients treated with doses >21 mg/kg/day	5-10 mg/kg/day In patients treated with doses >30 mg/kg/day		<2,500 µg/l
	- When target is reached			500-1,000 µg/l
Maximum dose	**28 mg/kg/day**	**40 mg/kg/day**		
Consider interruption				**<500 µg/l**

Starting dose

The recommended initial daily dose of EXJADE film-coated tablets is 14 mg/kg body weight.

An initial daily dose of 21 mg/kg may be considered for patients who require reduction of elevated body iron levels and who are also receiving more than 14 ml/kg/month of packed red blood cells (approximately >4 units/month for an adult).

An initial daily dose of 7 mg/kg may be considered for patients who do not require reduction of body iron levels and who are also receiving less than 7 ml/kg/month of packed red blood cells (approximately <2 units/month for an adult). The patient's response must be monitored and a dose increase should be considered if sufficient efficacy is not obtained (see section 5.1).

For patients already well managed on treatment with deferoxamine, a starting dose of EXJADE film-coated tablets that is numerically one third that of the deferoxamine dose could be considered (e.g. a patient receiving 40 mg/kg/day of deferoxamine for 5 days per week (or equivalent) could be transferred to a starting daily dose of 14 mg/kg/day of EXJADE film-coated tablets). When this results in a daily dose less than 14 mg/kg body weight, the patient's response must be monitored and a dose increase should be considered if sufficient efficacy is not obtained (see section 5.1).

Dose adjustment

It is recommended that serum ferritin be monitored every month and that the dose of EXJADE be adjusted, if necessary, every 3 to 6 months based on the trends in serum ferritin. Dose adjustments may be made in steps of 3.5 to 7 mg/kg and are to be tailored to the individual patient's response and therapeutic goals (maintenance or reduction of iron burden). In patients not adequately controlled with doses of 21 mg/kg (e.g. serum ferritin levels persistently above 2,500 µg/l and not showing a decreasing trend over time), doses of up to 28 mg/kg may be considered. The availability of long-term efficacy and safety data with EXJADE dispersible tablets used at doses above 30 mg/kg is currently limited (264 patients followed for an average of 1 year after dose escalation). If only very poor haemosiderosis control is achieved at doses up to 21 mg/kg, a further increase (to a maximum of 28 mg/kg) may not achieve satisfactory control, and alternative treatment options may be considered. If no satisfactory control is achieved at doses above 21 mg/kg, treatment at such doses should not be maintained and alternative treatment options should be considered whenever possible. Doses above 28 mg/kg are not recommended because there is only limited experience with doses above this level.

In patients treated with doses greater than 21 mg/kg, dose reductions in steps of 3.5 to 7 mg/kg should be considered when control has been achieved (e.g. serum ferritin levels persistently below 2,500 µg/l and showing a decreasing trend over time). In patients whose serum ferritin level has reached the target (usually between 500 and 1,000 µg/l), dose reductions in steps of 3.5 to 7 mg/kg should be considered to maintain serum ferritin levels within the target range. If serum ferritin falls consistently below 500 µg/l, an interruption of treatment should be considered (see section 4.4).

Non-transfusion-dependent thalassaemia syndromes

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 µg/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.

EXJADE film-coated tablets demonstrate higher bioavailability compared to the EXJADE dispersible tablet formulation (see section 5.2). In case of switching from dispersible tablets to film-coated tablets, the dose of the film-coated tablets should be 30% lower than the dose of the dispersible tablets, rounded to the nearest whole tablet.

The corresponding doses for both formulations are shown in the table below.

Table 2 Recommended doses for non-transfusion-dependent thalassaemia syndromes

	Film-coated tablets	**Dispersible tablets**	**Liver iron concentration (LIC)***		**Serum ferritin**
Starting dose	**7 mg/kg/day**	**10 mg/kg/day**	≥5 mg Fe/g dw	or	>800 µg/l
Monitoring					**Monthly**
Adjustment steps (every 3-6 months)	**Increase**		≥7 mg Fe/g dw	or	>2,000 µg/l
	3.5 - 7 mg/kg/day	5-10 mg/kg/day			
	Decrease		<7 mg Fe/g dw	or	≤2,000 µg/l
	3.5 - 7 mg/kg/day	5-10 mg/kg/day			
Maximum dose	**14 mg/kg/day**	**20 mg/kg/day**			
	7 mg/kg/day	**10 mg/kg/day**			
	For adults		not assessed	and	≤2,000 µg/l
	For paediatric patients				
Interruption			**<3 mg Fe/g dw**	or	**<300 µg/l**
Retreatment			**Not recommended**		

*LIC is the preferred method of iron overload determination.

Starting dose

The recommended initial daily dose of EXJADE film-coated tablets in patients with non-transfusion-dependent thalassaemia syndromes is 7 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 3.5 to 7 mg/kg should be considered if the patient's LIC is ≥7 mg Fe/g dw, or if serum ferritin is consistently >2,000 µg/l and not showing a downward trend, and the patient is tolerating the medicinal product well. Doses above 14 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 ≤2,000 µg/l, dosing should not exceed 7 mg/kg.

For patients in whom the dose was increased to >7 mg/kg, dose reduction to 7 mg/kg or less is recommended when LIC is <7 mg Fe/g dw or serum ferritin is ≤2,000 µg/l.

Treatment cessation
Once a satisfactory body iron level has been achieved (LIC <3 mg Fe/g dw or serum ferritin <300 µg/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.

Special populations

Elderly patients (≥65 years of age)

The dosing recommendations for elderly patients are the same as described above. In clinical studies, elderly patients experienced a higher frequency of adverse reactions than younger patients (in particular, diarrhoea) and should be monitored closely for adverse reactions that may require a dose adjustment.

Paediatric population

Transfusional iron overload:
The dosing recommendations for paediatric patients aged 2 to 17 years with transfusional iron overload are the same as for adult patients. Changes in weight of paediatric patients over time must be taken into account when calculating the dose.

In children with transfusional iron overload aged between 2 and 5 years, exposure is lower than in adults (see section 5.2). This age group may therefore require higher doses than are necessary in adults. However, the initial dose should be the same as in adults, followed by individual titration.

Non-transfusion-dependent thalassaemia syndromes:
In paediatric patients with non-transfusion-dependent thalassaemia syndromes, dosing should not exceed 7 mg/kg. In these patients, closer monitoring of LIC and serum ferritin

is essential to avoid overchelation: in addition to monthly serum ferritin assessments, LIC should be monitored every three months when serum ferritin is ≤800 µg/l.

Children from birth to 23 months:
The safety and efficacy of EXJADE in children from birth to 23 months of age have not been established. No data are available.

Patients with renal impairment

EXJADE has not been studied in patients with renal impairment and is contraindicated in patients with estimated creatinine clearance <60 ml/min (see sections 4.3 and 4.4).

Patients with hepatic impairment

EXJADE is not recommended in patients with severe hepatic impairment (Child-Pugh Class C). In patients with moderate hepatic impairment (Child-Pugh Class B), the dose should be considerably reduced followed by progressive increase up to a limit of 50% (see sections 4.4 and 5.2), and EXJADE must be used with caution in such patients. Hepatic function in all patients should be monitored before treatment, every 2 weeks during the first month and then every month (see section 4.4).

Method of administration
For oral use.
The film-coated tablets should be swallowed whole with some water. For patients who are unable to swallow whole tablets, the film-coated tablets may be crushed and administered by sprinkling the full dose onto soft food, e.g. yogurt or apple sauce (pureed apple). The dose should be immediately and completely consumed, and not stored for future use.

The film-coated tablets should be taken once a day, preferably at the same time each day, and may be taken on an empty stomach or with a light meal (see sections 4.5 and 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Combination with other iron chelator therapies as the safety of such combinations has not been established (see section 4.5).

Patients with estimated creatinine clearance <60 ml/min.

4.4 Special warnings and precautions for use

Renal function

Deferasirox has been studied only in patients with baseline serum creatinine within the age-appropriate normal range.

During clinical studies, increases in serum creatinine of >33% on ≥2 consecutive occasions, sometimes above the upper limit of the normal range, occurred in about 36% of patients. These were dose-dependent. About two-thirds of the patients showing serum creatinine increase returned below the 33% level without dose adjustment. In the remaining third the serum creatinine increase did not always respond to a dose reduction or a dose interruption. In some cases, only a stabilisation of the serum creatinine values has been observed after dose reduction. Cases of acute renal failure have been reported following post-marketing use of deferasirox (see section 4.8). In some post-marketing cases, renal function deterioration has led to renal failure requiring temporary or permanent dialysis.

The causes of the rises in serum creatinine have not been elucidated. Particular attention should therefore be paid to monitoring of serum creatinine in patients who are concomitantly receiving medicinal products that depress renal function, and in patients who are receiving high doses of deferasirox and/or low rates of transfusion (<7 ml/kg/month of packed red blood cells or <2 units/month for an adult). While no increase in renal adverse events was observed after dose escalation of EXJADE dispersible tablets to doses above 30 mg/kg in clinical studies, an increased risk of renal adverse events with film-coated tablets doses above 21 mg/kg cannot be excluded.

It is recommended that serum creatinine be assessed in duplicate before initiating therapy. **Serum creatinine, creatinine clearance** (estimated with the Cockcroft-Gault or MDRD formula in adults and with the Schwartz formula in children) and/or plasma cystatin C levels **should be monitored prior to therapy, weekly in the first month after initiation or modification of therapy with EXJADE, and monthly thereafter**. Patients with pre-existing renal conditions and patients who are receiving medicinal products that depress renal function may be more at risk of complications. Care should be taken to maintain adequate hydration in patients who develop diarrhoea or vomiting.

There have been post-marketing reports of metabolic acidosis occurring during treatment with deferasirox. The majority of these patients had renal impairment, renal tubulopathy (Fanconi syndrome) or diarrhoea, or conditions where acid-base imbalance is a known complication. Acid-base balance should be monitored as clinically indicated in these populations. Interruption of EXJADE therapy should be considered in patients who develop metabolic acidosis.

Table 3 Dose adjustment and interruption of treatment for renal monitoring

	Serum creatinine		**Creatinine clearance**
Before initiation of therapy	Twice (2x)	and	Once (1x)
Contraindicated			**<60 ml/min**
Monitoring			
- First month after start of therapy or dose modification	Weekly	and	Weekly
- Thereafter	Monthly	and	Monthly
Reduction of daily dose by 7 mg/kg/day (film-coated tablet formulation), *if following renal parameters are observed at **two** consecutive visits and cannot be attributed to other causes*			
Adult patients	>33% above pre-treatment average	and	Decreases <LLN* (<90 ml/min)
Paediatric patients	> age appropriate ULN**	and/or	Decreases <LLN* (<90 ml/min)
After dose reduction, interrupt treatment, if			
Adult and paediatric	Remains >33% above pre-treatment average	and/or	Decreases <LLN* (<90 ml/min)

*LLN: lower limit of the normal range

**ULN: upper limit of the normal range

Treatment may be reinitiated depending on the individual clinical circumstances.

Dose reduction or interruption may be also considered if abnormalities occur in levels of markers of renal tubular function and/or as clinically indicated:

- Proteinuria (test should be performed prior to therapy and monthly thereafter)
- Glycosuria in non-diabetics and low levels of serum potassium, phosphate, magnesium or urate, phosphaturia, aminoaciduria (monitor as needed).

Renal tubulopathy has been mainly reported in children and adolescents with beta-thalassaemia treated with EXJADE.

Patients should be referred to a renal specialist, and further specialised investigations (such as renal biopsy) may be considered if the following occur despite dose reduction and interruption:

- Serum creatinine remains significantly elevated and
- Persistent abnormality in another marker of renal function (e.g. proteinuria, Fanconi Syndrome).

Hepatic function

Liver function test elevations have been observed in patients treated with deferasirox. Post-marketing cases of hepatic failure, sometimes fatal, have been reported in patients treated with deferasirox. Most reports of hepatic failure involved patients with significant morbidities including pre-existing liver cirrhosis. However, the role of deferasirox as a contributing or aggravating factor cannot be excluded (see section 4.8).

It is recommended that serum transaminases, bilirubin and alkaline phosphatase be checked before the initiation of treatment, every 2 weeks during the first month and monthly thereafter. If there is a persistent and progressive increase in serum transaminase levels that cannot be attributed to other causes, EXJADE should be interrupted. Once the cause of the liver function test abnormalities has been clarified or after return to normal levels, cautious re-initiation of treatment at a lower dose followed by gradual dose escalation may be considered.

EXJADE is not recommended in patients with severe hepatic impairment (Child-Pugh Class C) (see section 5.2).

Summary of safety monitoring recommendations

Test	Frequency
Serum creatinine	In duplicate prior to therapy. Weekly during first month of therapy and during first month after dose modification. Monthly thereafter.
Creatinine clearance and/or plasma cystatin C	Prior to therapy. Weekly during first month of therapy and during first month after dose modification. Monthly thereafter.
Proteinuria	Prior to therapy. Monthly thereafter.
Other markers of renal tubular function (such as glycosuria in non-diabetics and low levels of serum potassium, phosphate, magnesium or urate, phosphaturia, aminoaciduria)	As needed.
Serum transaminases, bilirubin, alkaline phosphatase	Prior to therapy. Every 2 weeks during first month of therapy. Monthly thereafter.
Auditory and ophthalmic testing	Prior to therapy. Annually thereafter.
Body weight, height and sexual development	Prior to therapy. Annually in paediatric patients.

In patients with a short life expectancy (e.g. high-risk myelodysplastic syndromes), especially when co-morbidities could increase the risk of adverse events, the benefit of EXJADE might be limited and may be inferior to risks. As a consequence, treatment with EXJADE is not recommended in these patients.

Caution should be used in elderly patients due to a higher frequency of adverse reactions (in particular, diarrhoea).

Data in children with non-transfusion-dependent thalassaemia are very limited (see section 5.1). As a consequence, EXJADE therapy should be closely monitored to detect adverse reactions and to follow iron burden in the paediatric population. In addition, before treating heavily iron-overloaded children with non-transfusion-dependent thalassaemia with EXJADE, the physician should be aware that the consequences of long-term exposure in such patients are currently not known.

Gastrointestinal disorders

Upper gastrointestinal ulceration and haemorrhage have been reported in patients, including children and adolescents, receiving deferasirox. Multiple ulcers have been observed in some patients (see section 4.8). There have been reports of ulcers complicated with digestive perforation. Also, there have been reports of fatal gastrointestinal haemorrhages, especially in elderly patients who had haematological malignancies and/or low platelet counts. Physicians and patients should remain alert for signs and symptoms of gastrointestinal ulceration and haemorrhage during EXJADE therapy and promptly initiate additional evaluation and treatment if a serious gastrointestinal adverse reaction is suspected. Caution should be exercised in patients who are taking EXJADE in combination with substances that have known ulcerogenic potential, such as NSAIDs, corticosteroids, or oral bisphosphonates, in patients receiving anticoagulants and in patients with platelet counts below 50,000/mm^3 (50 x 10^9/l) (see section 4.5).

Skin disorders

Skin rashes may appear during EXJADE treatment. The rashes resolve spontaneously in most cases. When interruption of treatment may be necessary, treatment may be reintroduced after resolution of the rash, at a lower dose followed by gradual dose escalation. In severe cases this reintroduction could be conducted in combination with a short period of oral steroid administration. Cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported post marketing. The risk of other more severe skin reactions including DRESS (drug reaction with eosinophilia and systemic symptoms) cannot be excluded. If SJS or any other severe skin reaction is suspected, EXJADE should be discontinued immediately and should not be reintroduced.

Hypersensitivity reactions

Cases of serious hypersensitivity reactions (such as anaphylaxis and angioedema) have been reported in patients receiving deferasirox, with the onset of the reaction occurring in the majority of cases within the first month of treatment (see section 4.8). If such reactions occur, EXJADE should be discontinued and appropriate medical intervention instituted. Deferasirox should not be reintroduced in patients who have experienced a hypersensitivity reaction due to the risk of anaphylactic shock (see section 4.3).

Vision and hearing

Auditory (decreased hearing) and ocular (lens opacities) disturbances have been reported (see section 4.8). Auditory and ophthalmic testing (including fundoscopy) is recommended before the start of treatment and at regular intervals thereafter (every 12 months). If disturbances are noted during the treatment, dose reduction or interruption may be considered.

Blood disorders

There have been post-marketing reports of leukopenia, thrombocytopenia or pancytopenia (or aggravation of these cytopenias) and of aggravated anaemia in patients treated with deferasirox. Most of these patients had pre-existing haematological disorders that are frequently associated with bone marrow failure. However, a contributory or aggravating role cannot be excluded. Interruption of treatment should be considered in patients who develop unexplained cytopenia.

Other considerations

Monthly monitoring of serum ferritin is recommended in order to assess the patient's response to therapy (see section 4.2). If serum ferritin falls consistently below 500 µg/l (in transfusional iron overload) or below 300 µg/l (in non-transfusion-dependent thalassaemia syndromes), an interruption of treatment should be considered.

The results of the tests for serum creatinine, serum ferritin and serum transaminases

should be recorded and regularly assessed for trends.

In two clinical studies, growth and sexual development of paediatric patients treated with deferasirox for up to 5 years were not affected (see section 4.8). However, as a general precautionary measure in the management of paediatric patients with transfusional iron overload, body weight, height and sexual development should be monitored prior to therapy and at regular intervals (every 12 months).

Cardiac dysfunction is a known complication of severe iron overload. Cardiac function should be monitored in patients with severe iron overload during long-term treatment with EXJADE.

4.5 Interaction with other medicinal products and other forms of interaction

The safety of deferasirox in combination with other iron chelators has not been established. Therefore, it must not be combined with other iron chelator therapies (see section 4.3).

Interaction with food
The C_{max} of deferasirox film-coated tablets was increased (by 29%) when taken with a high-fat meal. EXJADE film-coated tablets may be taken either on an empty stomach or with a light meal, preferably at the same time each day (see sections 4.2 and 5.2).

Agents that may decrease EXJADE systemic exposure
Deferasirox metabolism depends on UGT enzymes. In a healthy volunteer study, the concomitant administration of deferasirox (single dose of 30 mg/kg, dispersible tablet formulation) and the potent UGT inducer, rifampicin, (repeated dose of 600 mg/day) resulted in a decrease of deferasirox exposure by 44% (90% CI: 37% - 51%). Therefore, the concomitant use of EXJADE with potent UGT inducers (e.g. rifampicin, carbamazepine, phenytoin, phenobarbital, ritonavir) may result in a decrease in EXJADE efficacy. The patient's serum ferritin should be monitored during and after the combination, and the dose of EXJADE adjusted if necessary.

Cholestyramine significantly reduced the deferasirox exposure in a mechanistic study to determine the degree of enterohepatic recycling (see section 5.2).

Interaction with midazolam and other agents metabolised by CYP3A4
In a healthy volunteer study, the concomitant administration of deferasirox dispersible tablets and midazolam (a CYP3A4 probe substrate) resulted in a decrease of midazolam exposure by 17% (90% CI: 8% - 26%). In the clinical setting, this effect may be more pronounced. Therefore, due to a possible decrease in efficacy, caution should be exercised when deferasirox is combined with substances metabolised through CYP3A4 (e.g. ciclosporin, simvastatin, hormonal contraceptive agents, bepridil, ergotamine).

Interaction with repaglinide and other agents metabolised by CYP2C8
In a healthy volunteer study, the concomitant administration of deferasirox as a moderate CYP2C8 inhibitor (30 mg/kg daily, dispersible tablet formulation), with repaglinide, a CYP2C8 substrate, given as a single dose of 0.5 mg, increased repaglinide AUC and C_{max} about 2.3-fold (90% CI [2.03-2.63]) and 1.6-fold (90% CI [1.42-1.84]), respectively. Since the interaction has not been established with dosages higher than 0.5 mg for repaglinide, the concomitant use of deferasirox with repaglinide should be avoided. If the combination appears necessary, careful clinical and blood glucose monitoring should be performed (see section 4.4). An interaction between deferasirox and other CYP2C8 substrates like paclitaxel cannot be excluded.

Interaction with theophylline and other agents metabolised by CYP1A2
In a healthy volunteer study, the concomitant administration of deferasirox as a CYP1A2 inhibitor (repeated dose of 30 mg/kg/day, dispersible tablet formulation) and the CYP1A2 substrate theophylline (single dose of 120 mg) resulted in an increase of theophylline AUC by 84% (90% CI: 73% to 95%). The single dose C_{max} was not affected, but an increase of theophylline C_{max} is expected to occur with chronic dosing. Therefore, the concomitant use of deferasirox with theophylline is not recommended. If deferasirox and theophylline are used concomitantly, monitoring of theophylline concentration and theophylline dose reduction should be considered. An interaction between deferasirox and other CYP1A2 substrates cannot be excluded. For substances that are predominantly metabolised by CYP1A2 and that have a narrow therapeutic index (e.g. clozapine, tizanidine), the same recommendations apply as for theophylline.

Other information

The concomitant administration of deferasirox and aluminium-containing antacid preparations has not been formally studied. Although deferasirox has a lower affinity for aluminium than for iron, it is not recommended to take deferasirox tablets with aluminium-containing antacid preparations.

The concomitant administration of deferasirox with substances that have known ulcerogenic potential, such as NSAIDs (including acetylsalicylic acid at high dosage), corticosteroids or oral bisphosphonates may increase the risk of gastrointestinal toxicity (see section 4.4). The concomitant administration of deferasirox with anticoagulants may also increase the risk of gastrointestinal haemorrhage. Close clinical monitoring is required when deferasirox is combined with these substances.

4.6 Fertility, pregnancy and lactation

Pregnancy

No clinical data on exposed pregnancies are available for deferasirox. Studies in animals have shown some reproductive toxicity at maternally toxic doses (see section 5.3). The potential risk for humans is unknown.

As a precaution, it is recommended that EXJADE is not used during pregnancy unless clearly necessary.

EXJADE may decrease the efficacy of hormonal contraceptives (see section 4.5). Women of childbearing potential are recommended to use additional or alternative non-hormonal methods of contraception when using EXJADE.

Breast-feeding

In animal studies, deferasirox was found to be rapidly and extensively secreted into maternal milk. No effect on the offspring was noted. It is not known if deferasirox is

secreted into human milk. Breast-feeding while taking EXJADE is not recommended.

Fertility
No fertility data is available for humans. In animals, no adverse effects on male or female fertility were found (see section 5.3).

4.7 Effects on ability to drive and use machines

EXJADE has minor influence on the ability to drive and use machines. Patients experiencing the uncommon adverse reaction of dizziness should exercise caution when driving or operating machines (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile
The most frequent reactions reported during chronic treatment with deferasirox dispersible tablets in adult and paediatric patients include gastrointestinal disturbances (mainly nausea, vomiting, diarrhoea or abdominal pain) and skin rash. Diarrhoea is reported more commonly in paediatric patients aged 2 to 5 years and in the elderly. These reactions are dose-dependent, mostly mild to moderate, generally transient and mostly resolve even if treatment is continued.

During clinical studies dose-dependent increases in serum creatinine occurred in about 36% of patients, though most remained within the normal range. Decreases in mean creatinine clearance have been observed in both paediatric and adult patients with beta-thalassemia and iron overload during the first year of treatment, but there is evidence that this does not decrease further in subsequent years of treatment. Elevations of liver transaminases have been reported. Safety monitoring schedules for renal and liver parameters are recommended. Auditory (decreased hearing) and ocular (lens opacities) disturbances are uncommon, and yearly examinations are also recommended (see section 4.4).

Tabulated list of adverse reactions
Adverse reactions are ranked below using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 4

Blood and lymphatic system disorders		
	Not known:	**Pancytopenia[1], thrombocytopenia[1], anaemia aggravated[1], neutropenia[1]**
Immune system disorders		
	Not known:	**Hypersensitivity reactions (including anaphylactic reactions and angioedema)[1]**
Metabolism and nutrition disorders		
	Not known:	**Metabolic acidosis[1]**
Psychiatric disorders		
	Uncommon:	**Anxiety, sleep disorder**
Nervous system disorders		
	Common:	**Headache**
	Uncommon:	**Dizziness**
Eye disorders		
	Uncommon:	**Cataract, maculopathy**
	Rare:	**Optic neuritis**
Ear and labyrinth disorders		
	Uncommon:	**Deafness**
Respiratory, thoracic and mediastinal disorders		
	Uncommon:	**Laryngeal pain**
Gastrointestinal disorders		
	Common:	**Diarrhoea, constipation, vomiting, nausea, abdominal pain, abdominal distension, dyspepsia**
	Uncommon:	**Gastrointestinal haemorrhage, gastric ulcer (including multiple ulcers), duodenal ulcer, gastritis**
	Rare:	**Oesophagitis**
	Not known:	**Gastrointestinal perforation[1], acute pancreatitis[1]**
Hepatobiliary disorders		
	Common:	**Transaminases increased**
	Uncommon:	**Hepatitis, cholelithiasis**
	Not known:	**Hepatic failure[1]**
Skin and subcutaneous tissue disorders		
	Common:	**Rash, pruritus**
	Uncommon:	**Pigmentation disorder**
	Not known:	**Stevens-Johnson syndrome[1], hypersensitivity vasculitis[1], urticaria[1], erythema multiforme[1], alopecia[1], toxic epidermal necrolysis (TEN)[1]**
Renal and urinary disorders		
	Very common:	**Blood creatinine increased**

	Common:	**Proteinuria**
	Uncommon:	**Renal tubular disorder (acquired Fanconi syndrome), glycosuria**
	Not known:	**Acute renal failure[1], tubulointerstitial nephritis[1], nephrolithiasis[1], renal tubular necrosis[1]**
General disorders and administration site conditions		
	Uncommon:	**Pyrexia, oedema, fatigue**

[1] Adverse reactions reported during post-marketing experience. These are derived from spontaneous reports for which it is not always possible to reliably establish frequency or a causal relationship to exposure to the medicinal product.

Description of selected adverse reactions
Gallstones and related biliary disorders were reported in about 2% of patients. Elevations of liver transaminases were reported as an adverse reaction in 2% of patients. Elevations of transaminases greater than 10 times the upper limit of the normal range, suggestive of hepatitis, were uncommon (0.3%). During post-marketing experience, hepatic failure, sometimes fatal, has been reported with the deferasirox dispersible tablet formulation, especially in patients with pre-existing liver cirrhosis (see section 4.4). There have been post-marketing reports of metabolic acidosis. The majority of these patients had renal impairment, renal tubulopathy (Fanconi syndrome) or diarrhoea, or conditions where acid-base imbalance is a known complication (see section 4.4). Cases of serious acute pancreatitis were observed without documented underlying biliary conditions. As with other iron chelator treatment, high-frequency hearing loss and lenticular opacities (early cataracts) have been uncommonly observed in patients treated with deferasirox (see section 4.4).

Creatinine clearance in transfusional iron overload

In a retrospective meta-analysis of 2,102 adult and paediatric beta-thalassaemia patients with transfusional iron overload treated with deferasirox dispersible tablets in two randomised and four open label studies of up to five years' duration, a mean creatinine clearance decrease of 13.2% in adult patients (95% CI: -14.4% to -12.1%; n=935) and 9.9% (95% CI: -11.1% to -8.6%; n=1,142) in paediatric patients was observed during the first year of treatment. In 250 patients who were followed for up to five years, no further decrease in mean creatinine clearance levels was observed.

Clinical study in patients with non-transfusion-dependent thalassaemia syndromes

In a 1-year study in patients with non-transfusion-dependent thalassaemia syndromes and iron overload (dispersible tablets at a dose of 10 mg/kg/day), diarrhoea (9.1%), rash (9.1%), and nausea (7.3%) were the most frequent study drug-related adverse events. Abnormal serum creatinine and creatinine clearance values were reported in 5.5% and 1.8% of patients, respectively. Elevations of liver transaminases greater than 2 times the baseline and 5 times the upper limit of normal were reported in 1.8% of patients.

Paediatric population
In two clinical studies, growth and sexual development of paediatric patients treated with deferasirox for up to 5 years were not affected (see section 4.4).

In a 5-year observational study in which 267 children aged 2 to <6 years (at enrollment) with transfusional haemosiderosis received deferasirox, there were no clinically meaningful differences in the safety and tolerability profile of Exjade in paediatric patients aged 2 to <6 years compared to the overall adult and older paediatric population, including increases in serum creatinine of >33% and above the upper limit of normal on ≥2 consecutive occasions (3.1%), and elevation of alanine aminotransferase (ALT) greater than 5 times the upper limit of normal (4.3%). Single events of increase in ALT and aspartate aminotransferase were reported in 20.0% and 8.3%, respectively, of the 145 patients who completed the study.

Diarrhoea is reported more commonly in paediatric patients aged 2 to 5 years than in older patients.

Renal tubulopathy has been mainly reported in children and adolescents with beta-thalassaemia treated with deferasirox. In post-marketing reports, a high proportion of cases of metabolic acidosis occurred in children in the context of Fanconi syndrome.

Acute pancreatitis has been reported, particularly in children and adolescents.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system

ADR Reporting Website: www.medicinesauthority.gov.mt/adrportal

4.9 Overdose

Cases of overdose (2-3 times the prescribed dose for several weeks) have been reported. In one case, this resulted in subclinical hepatitis which resolved after a dose interruption. Single doses of 80 mg/kg of the deferasirox dispersible tablet formulation (corresponding to a dose of 56 mg/kg film-coated tablets) in iron-overloaded thalassaemic patients caused mild nausea and diarrhoea.

Acute signs of overdose may include nausea, vomiting, headache and diarrhoea. Overdose may be treated by induction of emesis or by gastric lavage, and by symptomatic treatment.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Iron chelating agents, ATC code: V03AC03

Mechanism of action
Deferasirox is an orally active chelator that is highly selective for iron (III). It is a tridentate ligand that binds iron with high affinity in a 2:1 ratio. Deferasirox promotes excretion of

iron, primarily in the faeces. Deferasirox has low affinity for zinc and copper, and does not cause constant low serum levels of these metals.

Pharmacodynamic effects
In an iron-balance metabolic study in iron-overloaded adult thalassaemic patients, deferasirox at daily doses of 10, 20 and 40 mg/kg (dispersible tablet formulation) induced the mean net excretion of 0.119, 0.329 and 0.445 mg Fe/kg body weight/day, respectively.

Clinical efficacy and safety
Clinical efficacy studies were conducted with deferasirox dispersible tablets.

Deferasirox has been investigated in 411 adult (age ≥16 years) and 292 paediatric patients (aged 2 to <16 years) with chronic iron overload due to blood transfusions. Of the paediatric patients 52 were aged 2 to 5 years. The underlying conditions requiring transfusion included beta-thalassaemia, sickle cell disease and other congenital and acquired anaemias (myelodysplastic syndromes, Diamond-Blackfan syndrome, aplastic anaemia and other very rare anaemias).

Daily treatment with the deferasirox dispersible tablet formulation at doses of 20 and 30 mg/kg for one year in frequently transfused adult and paediatric patients with beta-thalassaemia led to reductions in indicators of total body iron; liver iron concentration was reduced by about -0.4 and -8.9 mg Fe/g liver (biopsy dry weight (dw)) on average, respectively, and serum ferritin was reduced by about -36 and -926 µg/l on average, respectively. At these same doses the ratios of iron excretion : iron intake were 1.02 (indicating net iron balance) and 1.67 (indicating net iron removal), respectively. Deferasirox induced similar responses in iron-overloaded patients with other anaemias. Daily doses of 10 mg/kg (dispersible tablet formulation)for one year could maintain liver iron and serum ferritin levels and induce net iron balance in patients receiving infrequent transfusions or exchange transfusions. Serum ferritin assessed by monthly monitoring reflected changes in liver iron concentration indicating that trends in serum ferritin can be used to monitor response to therapy. Limited clinical data (29 patients with normal cardiac function at baseline) using MRI indicate that treatment with deferasirox 10-30 mg/kg/day (dispersible tablet formulation) for 1 year may also reduce levels of iron in the heart (on average, MRI T2* increased from 18.3 to 23.0 milliseconds).

The principal analysis of the pivotal comparative study in 586 patients suffering from beta-thalassaemia and transfusional iron overload did not demonstrate non-inferiority of deferasirox dispersible tablets to deferoxamine in the analysis of the total patient population. It appeared from a post-hoc analysis of this study that, in the subgroup of patients with liver iron concentration ≥7 mg Fe/g dw treated with deferasirox dispersible tablets (20 and 30 mg/kg) or deferoxamine (35 to ≥50 mg/kg), the non-inferiority criteria were achieved. However, in patients with liver iron concentration <7 mg Fe/g dw treated with deferasirox dispersible tablets (5 and 10 mg/kg) or deferoxamine (20 to 35 mg/kg), non-inferiority was not established due to imbalance in the dosing of the two chelators. This imbalance occurred because patients on deferoxamine were allowed to remain on their pre-study dose even if it was higher than the protocol specified dose.
Fifty-six patients under the age of 6 years participated in this pivotal study, 28 of them receiving deferasirox dispersible tablets.

It appeared from preclinical and clinical studies that deferasirox dispersible tablets could be as active as deferoxamine when used in a dose ratio of 2:1 (i.e. a dose of deferasirox dispersible tablets that is numerically half of the deferoxamine dose). For deferasirox film-coated tablets, a dose ratio of 3:1 can be considered (i.e. a dose of deferasirox film-coated tablets that is numerically one third of the deferoxamine dose). However, this dosing recommendation was not prospectively assessed in the clinical studies.

In addition, in patients with liver iron concentration ≥7 mg Fe/g dw with various rare anaemias or sickle cell disease, deferasirox dispersible tablets up to 20 and 30 mg/kg produced a decrease in liver iron concentration and serum ferritin comparable to that obtained in patients with beta-thalassaemia.

In patients with non-transfusion-dependent thalassaemia syndromes and iron overload, treatment with deferasirox dispersible tablets was assessed in a 1-year, randomised, double-blind, placebo-controlled study. The study compared the efficacy of two different deferasirox dispersible tablet regimens (starting doses of 5 and 10 mg/kg/day, 55 patients in each arm) and of matching placebo (56 patients). The study enrolled 145 adult and 21 paediatric patients. The primary efficacy parameter was the change in liver iron concentration (LIC) from baseline after 12 months of treatment. One of the secondary efficacy parameters was the change in serum ferritin between baseline and fourth quarter. At a starting dose of 10 mg/kg/day, deferasirox dispersible tablets led to reductions in indicators of total body iron. On average, liver iron concentration decreased by 3.80 mg Fe/g dw in patients treated with deferasirox dispersible tablets (starting dose 10 mg/kg/day) and increased by 0.38 mg Fe/g dw in patients treated with placebo ($p<0.001$). On average, serum ferritin decreased by 222.0 µg/l in patients treated with deferasirox dispersible tablets (starting dose 10 mg/kg/day) and increased by 115 µg/l in patients treated with placebo ($p<0.001$).

The European Medicines Agency has deferred the obligation to submit the results of studies with EXJADE in one or more subsets of the paediatric population in the treatment of chronic iron overload requiring chelation therapy (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

EXJADE film-coated tablets demonstrate higher bioavailability compared to the EXJADE dispersible tablet formulation. After adjustment of the strength, the film-coated tablet formulation (360 mg strength) was equivalent to EXJADE dispersible tablets (500 mg strength) with respect to the mean area under the plasma concentration time curve (AUC) under fasting conditions. The C_{max} was increased by 30% (90% CI: 20.3% - 40.0%); however a clinical exposure/response analysis revealed no evidence of clinically relevant effects of such an increase.

Absorption

Deferasirox (dispersible tablet formulation) is absorbed following oral administration with a median time to maximum plasma concentration (t_{max}) of about 1.5 to 4 hours. The absolute bioavailability (AUC) of deferasirox (dispersible tablet formulation) is about 70% compared to an intravenous dose. The absolute bioavailability of the film-coated tablet formulation has not been determined. Bioavailability of deferasirox film-coated tablets was 36% greater than that with dispersible tablets.

A food-effect study involving administration of the film-coated tablets to healthy volunteers under fasting conditions and with a low-fat (fat content <10% of calories) or high-fat (fat content >50% of calories) meal indicated that the AUC and C_{max} were slightly decreased after a low-fat meal (by 11% and 16%, respectively). After a high-fat meal, AUC and C_{max} were increased (by 18% and 29%, respectively). The increases in C_{max} due to the change in formulation and due to the effect of a high-fat meal may be additive and therefore, it is recommended that the film-coated tablets should be taken either on an empty stomach or with a light meal.

Distribution
Deferasirox is highly (99%) protein bound to plasma proteins, almost exclusively serum albumin, and has a small volume of distribution of approximately 14 litres in adults.

Biotransformation
Glucuronidation is the main metabolic pathway for deferasirox, with subsequent biliary excretion. Deconjugation of glucuronidates in the intestine and subsequent reabsorption (enterohepatic recycling) is likely to occur: in a healthy volunteer study, the administration of cholestyramine after a single dose of deferasirox resulted in a 45% decrease in deferasirox exposure (AUC).

Deferasirox is mainly glucuronidated by UGT1A1 and to a lesser extent UGT1A3. CYP450-catalysed (oxidative) metabolism of deferasirox appears to be minor in humans (about 8%). No inhibition of deferasirox metabolism by hydroxyurea was observed *in vitro*.

Elimination
Deferasirox and its metabolites are primarily excreted in the faeces (84% of the dose). Renal excretion of deferasirox and its metabolites is minimal (8% of the dose). The mean elimination half-life ($t_{1/2}$) ranged from 8 to 16 hours. The transporters MRP2 and MXR (BCRP) are involved in the biliary excretion of deferasirox.

Linearity / non-linearity
The C_{max} and AUC_{0-24h} of deferasirox increase approximately linearly with dose under steady-state conditions. Upon multiple dosing exposure increased by an accumulation factor of 1.3 to 2.3.

Characteristics in patients
Paediatric patients
The overall exposure of adolescents (12 to ≤17 years) and children (2 to <12 years) to deferasirox after single and multiple doses was lower than that in adult patients. In children younger than 6 years old exposure was about 50% lower than in adults. Since dosing is individually adjusted according to response this is not expected to have clinical consequences.

Gender
Females have a moderately lower apparent clearance (by 17.5%) for deferasirox compared to males. Since dosing is individually adjusted according to response this is not expected to have clinical consequences.

Elderly patients
The pharmacokinetics of deferasirox have not been studied in elderly patients (aged 65 or older).

Renal or hepatic impairment
The pharmacokinetics of deferasirox have not been studied in patients with renal impairment. The pharmacokinetics of deferasirox were not influenced by liver transaminase levels up to 5 times the upper limit of the normal range.

In a clinical study using single doses of 20 mg/kg deferasirox dispersible tablets, the average exposure was increased by 16% in subjects with mild hepatic impairment (Child-Pugh Class A) and by 76% in subjects with moderate hepatic impairment (Child-Pugh Class B) compared to subjects with normal hepatic function. The average C_{max} of deferasirox in subjects with mild or moderate hepatic impairment was increased by 22%. Exposure was increased 2.8-fold in one subject with severe hepatic impairment (Child-Pugh Class C) (see sections 4.2 and 4.4).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans, based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity or carcinogenic potential. The main findings were kidney toxicity and lens opacity (cataracts). Similar findings were observed in neonatal and juvenile animals. The kidney toxicity is considered mainly due to iron deprivation in animals that were not previously overloaded with iron.

Tests of genotoxicity *in vitro* were negative (Ames test, chromosomal aberration test) while deferasirox caused formation of micronuclei *in vivo* in the bone marrow, but not liver, of non-iron-loaded rats at lethal doses. No such effects were observed in iron-preloaded rats. Deferasirox was not carcinogenic when administered to rats in a 2-year study and transgenic p53+/- heterozygous mice in a 6-month study.

The potential for toxicity to reproduction was assessed in rats and rabbits. Deferasirox was not teratogenic, but caused increased frequency of skeletal variations and stillborn pups in rats at high doses that were severely toxic to the non-iron-overloaded mother. Deferasirox did not cause other effects on fertility or reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Cellulose, microcrystalline
Crospovidone
Povidone (K30)
Magnesium stearate
Silica, colloidal anhydrous
Poloxamer 188

Coating material:
Hypromellose
Titanium dioxide (E171)
Macrogol (4000)
Talc
Indigo carmine aluminium lake (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PVDC/Aluminium blisters.

Unit packs containing 30 or 90 film-coated tablets or multipacks containing 300 (10 packs of 30) film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EXJADE 90 mg film-coated tablets
EU/1/06/356/011
EU/1/06/356/012
EU/1/06/356/013

EXJADE 180 mg film-coated tablets
EU/1/06/356/014
EU/1/06/356/015
EU/1/06/356/016

EXJADE 360 mg film-coated tablets
EU/1/06/356/017
EU/1/06/356/018
EU/1/06/356/019

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28 August 2006
Date of latest renewal: 18 April 2016

10. DATE OF REVISION OF THE TEXT

6 October 2016

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

Package leaflet: Information for the user

EXJADE 90 mg film-coated tablets
EXJADE 180 mg film-coated tablets
EXJADE 360 mg film-coated tablets

Deferasirox

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed only for you or your child. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What EXJADE is and what it is used for

What EXJADE is

EXJADE contains an active substance called deferasirox. It is an iron chelator which is a medicine used to remove the excess iron from the body (also called iron overload). It

traps and removes excess iron which is then excreted mainly in the stools.

What EXJADE is used for

Repeated blood transfusions may be necessary in patients with various types of anaemia (for example thalassaemia, sickle cell disease or myelodysplastic syndromes (MDS)). However, repeated blood transfusions can cause a build-up of excess iron. This is because blood contains iron and your body does not have a natural way to remove the excess iron you get with your blood transfusions. In patients with non-transfusion-dependent thalassaemia syndromes, iron overload may also develop over time, mainly due to increased absorption of dietary iron in response to low blood cell counts. Over time, the excess iron can damage important organs such as the liver and heart. Medicines called *iron chelators* are used to remove the excess iron and reduce the risk of it causing organ damage.

EXJADE is used to treat chronic iron overload caused by frequent blood transfusions in patients with beta thalassaemia major aged 6 years and older.

EXJADE is also used to treat chronic iron overload when deferoxamine therapy is contraindicated or inadequate in patients with beta thalassaemia major with iron overload caused by infrequent blood transfusions, in patients with other types of anaemias, and in children aged 2 to 5 years.

EXJADE is also used when deferoxamine therapy is contraindicated or inadequate to treat patients aged 10 years or older who have iron overload associated with their thalassaemia syndromes, but who are not transfusion dependent.

2. What you need to know before you take EXJADE

Do not take EXJADE

- if you are allergic to deferasirox or any of the other ingredients of this medicine (listed in section 6). If this applies to you, **tell your doctor before taking EXJADE**. If you think you may be allergic, ask your doctor for advice.
- if you have moderate or severe kidney disease.
- if you are currently taking any other iron chelator medicines.

EXJADE is not recommended

- if you are at an advanced stage of myelodysplastic syndrome (MDS; decreased production of blood cells by the bone marrow) or have advanced cancer.

Warnings and precautions

Talk to your doctor or pharmacist before taking EXJADE:

- if you have a kidney or liver problem.
- if you have a cardiac problem due to iron overload.
- if you notice a marked decrease in your urine output (sign of kidney problem).
- if you develop a severe rash, or difficulty breathing and dizziness or swelling mainly of the face and throat (signs of severe allergic reaction, see also section 4 “Possible side effects”).
- if you develop a rash, red skin, blistering of the lips, eyes or mouth, skin peeling, fever (signs of severe skin reaction, see also section 4 “Possible side effects”).
- if you experience a combination of drowsiness, upper right abdominal pain, yellowing or increased yellowing of your skin or eyes and dark urine (signs of liver problems).
- if you vomit blood and/or have black stools.
- if you experience frequent abdominal pain, particularly after eating or taking EXJADE.
- if you experience frequent heartburn.
- if you have a low level of platelets or white blood cells in your blood test.
- if you have blurred vision
- if you have diarrhoea or vomiting.

If any of these apply to you, tell your doctor straight away.

Monitoring your EXJADE treatment
You will have regular blood and urine tests during treatment. These will monitor the amount of iron in your body (blood level of *ferritin*) to see how well EXJADE is working. The tests will also monitor your kidney function (blood level of creatinine, presence of protein in the urine) and liver function (blood level of transaminases). Your doctor may require you to undergo a kidney biopsy, if he/she suspects significant kidney damage. You may also have MRI (magnetic resonance imaging) tests to determine the amount of iron in your liver. Your doctor will take these tests into consideration when deciding on the dose of EXJADE most suitable for you and will also use these tests to decide when you should stop taking EXJADE.

Your eyesight and hearing will be tested each year during treatment as a precautionary measure.

Other medicines and EXJADE

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes in particular:

- other iron chelators, which must not be taken with EXJADE,
- antatacids (medicines used to treat heartburn) containing aluminium, which should not be taken at the same time of day as EXJADE,
- ciclosporin (used to prevent the body rejecting a transplanted organ or for other conditions, such as rheumatoid arthritis or atopic dermatitis),
- simvastatin (used to lower cholesterol),
- certain painkillers or anti-inflammatory medicines (e.g. aspirin, ibuprofen, corticosteroids),
- oral bisphosphonates (used to treat osteoporosis),
- anticoagulant medicines (used to prevent or treat blood clotting),
- hormonal contraceptive agents (birth control medicines),
- bepridil, ergotamine (used for heart problems and migraines),
- repaglinide (used to treat diabetes),

- rifampicin (used to treat tuberculosis),
- phenytoin, phenobarbital, carbamazepine (used to treat epilepsy),
- ritonavir (used in the treatment of HIV infection),
- paclitaxel (used in cancer treatment),
- theophylline (used to treat respiratory diseases such as asthma),
- clozapine (used to treat psychiatric disorders such as schizophrenia),
- tizanidine (used as a muscle relaxant),
- cholestyramine (used to lower cholesterol levels in the blood).

Additional tests may be required to monitor the blood levels of some of these medicines.

Older people (age 65 years and over)

EXJADE can be used by people aged 65 years and over at the same dose as for other adults. Elderly patients may experience more side effects (in particular diarrhoea) than younger patients. They should be monitored closely by their doctor for side effects that may require a dose adjustment.

Children and adolescents

EXJADE can be used in children and adolescents receiving regular blood transfusions aged 2 years and over and in children and adolescents not receiving regular blood transfusions aged 10 years and over. As the patient grows the doctor will adjust the dose.

EXJADE is not recommended for children aged under 2 years.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

EXJADE is not recommended during pregnancy unless clearly necessary.

If you are currently using an oral contraceptive or using a patch contraceptive to prevent pregnancy, you should use an additional or different type of contraception (e.g. condom), as EXJADE may reduce the effectiveness of oral and patch contraceptives.

Breast-feeding is not recommended during treatment with EXJADE.

Driving and using machines

If you feel dizzy after taking EXJADE, do not drive or operate any tools or machines until you are feeling normal again.

3. How to take EXJADE

Treatment with EXJADE will be overseen by a doctor who is experienced in the treatment of iron overload caused by blood transfusions.

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

How much EXJADE to take

The dose of EXJADE is related to body weight for all patients. Your doctor will calculate the dose you need and tell you how many tablets to take each day.

- The usual daily dose for EXJADE film-coated tablets at the start of the treatment for patients receiving regular blood transfusions is 14 mg per kilogram body weight. A higher or lower starting dose may be recommended by your doctor based on your individual treatment needs.
- The usual daily dose for EXJADE film-coated tablets at the start of the treatment for patients not receiving regular blood transfusions is 7 mg per kilogram body weight.
- Depending on how you respond to treatment, your doctor may later adjust your treatment to a higher or lower dose.
- The maximum recommended daily dose for EXJADE film-coated tablets is:
  - 28 mg per kilogram body weight for patients receiving regular blood transfusions,
  - 14 mg per kilogram body weight for adult patients not receiving regular blood transfusions,
  - 7 mg per kilogram body weight for children and adolescents not receiving regular blood transfusions.

Deferasirox also comes as “dispersible” tablets. If you are switching from the dispersible tablets to these film-coated tablets, you will need an adjustment of the dose.

When to take EXJADE

- Take EXJADE once a day, every day, at about the same time each day with some water.
- Take EXJADE film-coated tablets either on an empty stomach or with a light meal.

Taking EXJADE at the same time each day will also help you remember when to take your tablets.

For patients who are unable to swallow whole tablets, EXJADE film-coated tablets may be crushed and taken by sprinkling the full dose onto soft food such as yogurt or apple sauce (pureed apple). The food should be immediately and completely consumed. Do not store it for future use.

How long to take EXJADE

Continue taking EXJADE every day for as long as your doctor tells you. This is a long-term treatment, possibly lasting for months or years. Your doctor will regularly monitor your condition to check that the treatment is having the desired effect (see also section 2: “Monitoring your EXJADE treatment”).

If you have questions about how long to take EXJADE, talk to your doctor.

If you take more EXJADE than you should

If you have taken too much EXJADE, or if someone else accidentally takes your tablets, contact your doctor or hospital for advice straight away. Show them the pack of tablets. Medical treatment may be necessary.

If you forget to take EXJADE

If you miss a dose, take it as soon as you remember on that day. Take your next dose as scheduled. Do not take a double dose on the next day to make up for the forgotten tablet(s).

If you stop taking EXJADE

Do not stop taking EXJADE unless your doctor tells you to. If you stop taking it, the excess iron will no longer be removed from your body (see also above section "How long to take EXJADE").

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Most of the side effects are mild to moderate and will generally disappear after a few days to a few weeks of treatment.

Some side effects could be serious and need immediate medical attention.

These side effects are uncommon (may affect up to 1 in 100 people) or rare (may affect up to 1 in 1,000 people).

- If you get a severe rash, or difficulty breathing and dizziness or swelling mainly of the face and throat (signs of severe allergic reaction),
- If you get a severe rash, red skin, blistering of the lips, eyes or mouth, skin peeling, fever,
- If you notice a marked decrease in your urine output (sign of kidney problem),
- If you experience a combination of drowsiness, upper right abdominal pain, yellowing or increased yellowing of your skin or eyes and dark urine (signs of liver problems),
- If you vomit blood and/or have black stools,
- If you experience frequent abdominal pain, particularly after eating or taking EXJADE,
- If you experience frequent heartburn,
- If you experience partial loss of vision,
- If you experience severe upper stomach pain (pancreatitis),

stop taking this medicine and tell your doctor straight away.

Some side effects could become serious.

These side effects are uncommon.

- If you get blurred or cloudy eyesight,
- If you get reduced hearing,

tell your doctor as soon as possible.

Other side effects

Very common (may affect more than 1 in 10 people)

- Disturbance in kidney function tests.

Common (may affect up to 1 in 10 people)

- Gastrointestinal disorders, such as nausea, vomiting, diarrhoea, pain in the abdomen, bloating, constipation, indigestion
- Rash
- Headache
- Disturbance in liver function tests
- Itching
- Disturbance in urine test (protein in the urine)

If any of these affects you severely, tell your doctor.

Uncommon (may affect up to 1 in 100 people)

- Dizziness
- Fever
- Sore throat
- Swelling of arms or legs
- Change in the colour of the skin
- Anxiety
- Sleep disorder
- Tiredness

If any of these affects you severely, tell your doctor.

Frequency not known (cannot be estimated from the available data).

- A decrease in the number of cells involved in blood clotting (thrombocytopenia), in the number of red blood cells (anaemia aggravated), in the number of white blood cells (neutropenia) or in the number of all kinds of blood cells (pancytopenia)
- Hair loss
- Kidney stones
- Low urine output
- Tear in stomach or intestine wall that can be painful and cause nausea
- Severe upper stomach pain (pancreatitis)
- Abnormal level of acid in blood

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the

national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store EXJADE

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the blister and the carton after EXP. The expiry date refers to the last day of that month.
- Do not use any pack that is damaged or shows signs of tampering.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What EXJADE contains

The active substance is deferasirox.

- Each film-coated tablet of EXJADE 90 mg contains 90 mg deferasirox.
- Each film-coated tablet of EXJADE 180 mg contains 180 mg deferasirox.
- Each film-coated tablet of EXJADE 360 mg contains 360 mg deferasirox.

The other ingredients are microcrystalline cellulose; crospovidone; povidone (K30); magnesium stearate; colloidal anhydrous silica and poloxamer 188. The tablet coating material contains: hypromellose; titanium dioxide (E171); macrogol (4000); talc; indigo carmine aluminium lake (E132).

What EXJADE looks like and contents of the pack

EXJADE is supplied as film-coated tablets. The film-coated tablets are ovaloid and biconvex.

- EXJADE 90 mg film-coated tablets are light blue and stamped “90” on one side and “NVR” on the other.
- EXJADE 180 mg film-coated tablets are medium blue and stamped “180” on one side and “NVR” on the other.
- EXJADE 360 mg film-coated tablets are dark blue and stamped “360” on one side and “NVR” on the other.

Each blister pack contains 30 or 90 film-coated tablets. The multipacks contain 300 (10 packs of 30) film-coated tablets.

Not all pack sizes or strengths may be available in your country.

Marketing Authorisation Holder

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

Manufacturer

Novartis Pharma GmbH
Roonstraße 25
D-90429 Nuremberg
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

België/Belgique/Belgien Novartis Pharma N.V. Tél/Tel: +32 2 246 16 11	**Lietuva** Novartis Pharma Services Inc. Tel: +370 5 269 16 50
България Novartis Pharma Services Inc. Тел.: +359 2 489 98 28	**Luxembourg/Luxemburg** Novartis Pharma N.V Tél/Tel: +32 2 246 16 11
Česká republika Novartis s.r.o. Tel: +420 225 775 111	**Magyarország** Novartis Hungária Kft. Pharma Tel.: +36 1 457 65 00
Danmark Novartis Healthcare A/S Tlf: +45 39 16 84 00	**Malta** Novartis Pharma Services Inc. Tel: +356 2122 2872
Deutschland Novartis Pharma GmbH Tel: +49 911 273 0	**Nederland** Novartis Pharma B.V. Tel: +31 26 37 82 555
Eesti Novartis Pharma Services Inc. Tel: +372 66 30 810	**Norge** Novartis Norge AS Tlf: +47 23 05 20 00
Ελλάδα Novartis (Hellas) A.E.B.E. Τηλ: +30 210 281 17 12	**Österreich** Novartis Pharma GmbH Tel: +43 1 86 6570
España Novartis Farmacéutica, S.A. Tel: +34 93 306 42 00	**Polska** Novartis Poland Sp. z o.o. Tel.: +48 22 375 4888
France Novartis Pharma S.A.S. Tél: +33 1 55 47 66 00	**Portugal** Novartis Farma - Produtos Farmacêuticos, S.A. Tel: +351 21 000 8600
Hrvatska Novartis Hrvatska d.o.o. Tel. +385 1 6274 220	**România** Novartis Pharma Services Romania SRL Tel: +40 21 31299 01
Ireland Novartis Ireland Limited Tel: +353 1 260 12 55	**Slovenija** Novartis Pharma Services Inc. Tel: +386 1 300 75 50
Ísland Vistor hf. Sími: +354 535 7000	**Slovenská republika** Novartis Slovakia s.r.o. Tel: +421 2 5542 5439

Italia Novartis Farma S.p.A. Tel: +39 02 96 54 1	**Suomi/Finland** Novartis Finland Oy Puh/Tel: +358 (0)10 6133 200
Κύπρος Novartis Pharma Services Inc. Τηλ: +357 22 690 690	**Sverige** Novartis Sverige AB Tel: +46 8 732 32 00
Latvija Novartis Pharma Services Inc. Tel: +371 67 887 070	**United Kingdom** Novartis Pharmaceuticals UK Ltd. Tel: +44 1276 698370

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu