הודעה על החמרה (מידע בטיחות) בעלון לרופא

(מעודכן 05.2013)

תאריך: 11.1.2017

שם תכשיר באנגלית ומספר הרישום:

Certican tablets 0.25mg, 0.5mg, 0.75mg

[132 60 31066] , [132 58 31064], [132 59 31065]

שם בעל הרישום: Novartis Israel Ltd.

ההחמרות המבוקשות		
פרק בעלון	**טקסט נוכחי**	**טקסט חדש**

Kidney and heart transplantation Certican® is indicated for the prophylaxis of organ rejection in adult patients at low to moderate immunological risk receiving an allogeneic renal or cardiac transplant. In kidney and heart transplantation, Certican should be used in combination with ciclosporin for microemulsion and corticosteroids. **Liver transplantation** Certican® is indicated for the prophylaxis of organ rejection in adult patients receiving a hepatic transplant. In liver transplantation, Certican should be used in combination with tacrolimus and corticosteroids.	**Kidney and heart transplantation** Certican® is indicated for the prophylaxis of organ rejection in adult patients at low to moderate immunological risk receiving an allogeneic renal or cardiac transplant. In kidney and heart transplantation, Certican should be used in combination with ciclosporin for microemulsion and corticosteroids. **Liver transplantation** Certican® is indicated for the prophylaxis of organ rejection in patients receiving a hepatic transplant. In liver transplantation, Certican should be used in combination with tacrolimus and corticosteroids.	**4.1 Therapeutic indications**
….. *Paediatric population* There is insufficient ~~experience~~ data in children and adolescents to recommend the use of Certican ~~in children and adolescents~~. ~~Limited information is available~~ in renal transplantation (see section 5.1 and 5.2) and no recommendation on a posology can be made. In hepatic transplant paediatric patients, Certican should not be used (see section 5.1). ….. Certican has a narrow therapeutic index which may require adjustments in dosing to maintain therapeutic response. Routine everolimus whole blood therapeutic drug concentration monitoring is recommended. Based on exposure-efficacy and exposure-safety analysis, patients achieving everolimus whole blood trough concentrations ³3.0 ng/ml have been found to have a lower incidence of biopsy-proven acute rejection in renal, cardiac and hepatic transplantation compared with patients whose trough concentrations are below 3.0 ng/ml. The recommended upper limit of the therapeutic range is 8 ng/ml. Exposure above 12 ng/ml has not been studied. These recommended ranges for everolimus are based on chromatographic methods. ….	….. *Paediatric population* There is insufficient experience to recommend the use of Certican in children and adolescents. Limited information is available in renal transplant paediatric patients (see section 5.2). …..	**4.2 Posology and method of administration**

….. Fertility There are literature reports of reversible azoospermia and oligospermia in patients treated with mTOR inhibitors (see section 4.4, 4.8, and 5.3). The potential for everolimus to cause infertility in male and female patients is unknown, however, male infertility and secondary amenorrhoea have been observed. …..	…. Fertility There are literature reports of reversible azoospermia and oligospermia in patients treated with mTOR inhibitors (see section 4.4, 4.8, and 5.3). …	**4.6** **Fertility, pregnancy and lactation**

…. a) Summary of the safety profile The frequencies of adverse reactions listed below are derived from analysis of the 12-month incidences of events reported in multicentre, randomised, controlled trials investigating Certican in combination with calcineurin inhibitors (CNI) and corticosteroids in adult transplant recipients. All but two of the trials (in renal transplantation) included non-Certican, CNI-based standard-therapy arms. Certican combined with ciclosporin was studied in five trials in renal transplant recipients totalling 2,497 patients (including two studies without a non-Certican control group), and three trials in heart transplant recipients totalling 1,531 patients (ITT populations, see section 5.1). Certican combined with tacrolimus was studied in one trial, which included 719 liver transplant recipients (ITT population, see section 5.1). The most common events are: infections, anaemia, hyperlipidaemia, new onset of diabetes mellitus, insomnia, headache, hypertension, cough, constipation, nausea, peripheral oedema, impaired healing (including pleural and pericardial effusion). The occurrence of the adverse events may depend on the immunosuppressive regimen (i.e. degree and duration). In the studies combining Certican with ciclosporin, elevated serum creatinine was observed more frequently in patients administered Certican in combination with full-dose ciclosporin for microemulsion than in control patients. The overall incidence of adverse events was lower with reduced-dose ciclosporin for microemulsion (see section 5.1). The safety profile of Certican administered with reduced-dose ciclosporin was similar to that described in the 3 pivotal studies in	… a) Summary of the safety profile The frequencies of adverse reactions listed below are derived from analysis of the 12-month incidences of events reported in multicentre, randomised, controlled trials investigating Certican in combination with calcineurin inhibitors (CNI) and corticosteroids in transplant recipients. All but two of the trials (in renal transplantation) included non-Certican, CNI-based standard-therapy arms. Certican combined with ciclosporin was studied in five trials in renal transplant recipients totalling 2,497 patients (including two studies without a non-Certican control group), and three trials in heart transplant recipients totalling 1,531 patients (ITT populations, see section 5.1). Certican combined with tacrolimus was studied in one trial, which included 719 liver transplant recipients (ITT population, see section 5.1). The most common events are: infections, anaemia, hyperlipidaemia, new onset of diabetes mellitus, insomnia, headache, hypertension, cough, constipation, nausea, peripheral oedema, impaired healing (including pleural and pericardial effusion). The occurrence of the adverse events may depend on the immunosuppressive regimen (i.e. degree and duration). In the studies combining Certican with ciclosporin, elevated serum creatinine was observed more frequently in patients administered Certican in combination with full-dose ciclosporin for microemulsion than in control patients. The overall incidence of adverse events was lower with reduced-dose ciclosporin for microemulsion (see section 5.1). The safety profile of Certican administered with reduced-dose ciclosporin was similar to that described in the 3 pivotal studies in	**4.8 Undesirable effects**

which full-dose ciclosporin was administered, except that elevation of serum creatinine was less frequent, and mean and median serum creatinine values were lower, than in the Phase III studies. b) Tabulated summary of adverse reactions Table 4 contains adverse drug reactions possibly or probably related to Certican seen in Phase III clinical trials. Unless noted otherwise, these disorders have been identified by an increased incidence in the Phase III studies comparing Certican-treated patients with patients on a non-Certican, standard-therapy regimen, or the same incidence in case the event is a known ADR of the comparator MPA in renal and heart transplant studies (see section 5.1). Except where noted otherwise, the adverse reaction profile is relatively consistent across all transplant indications. It is compiled according to MedDRA standard organ classes. *Adverse reactions are listed according to their frequencies, which are defined as: 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).* …… **Table 4** **Adverse drug reactions possibly or probably related to Certican** ***Reproductive system and breast disorders*** *Common* Erectile dysfunction, menstrual disorder (including amenorrhoea and menorrhagia) *Uncommon* Ovarian cyst …..	which full-dose ciclosporin was administered, except that elevation of serum creatinine was less frequent, and mean and median serum creatinine values were lower, than in the Phase III studies. b) Tabulated summary of adverse reactions Table 4 contains adverse drug reactions possibly or probably related to Certican seen in Phase III clinical trials. Unless noted otherwise, these disorders have been identified by an increased incidence in the Phase III studies comparing Certican-treated patients with patients on a non-Certican, standard-therapy regimen, or the same incidence in case the event is a known ADR of the comparator MPA in renal and heart transplant studies (see section 5.1). Except where noted otherwise, the adverse reaction profile is relatively consistent across all transplant indications. It is compiled according to MedDRA standard organ classes. *Adverse reactions are listed according to their frequencies, which are defined as: 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).* …. **Table 4** **Adverse drug reactions possibly or probably related to Certican** ***Reproductive system and breast disorders*** *Common* Erectile dysfunction ….	

…..	…..	**5.1 Pharmacodynamic properties**
Clinical efficacy and safety	Clinical efficacy and safety	
Renal transplantation		
Certican in fixed doses of 1.5 mg/day and 3 mg/day, in combination with standard doses of ciclosporin for microemulsion and corticosteroids, was investigated in two Phase III *de novo* adult renal transplant trials (B201 and B251). Mycophenolate mofetil (MMF) 1 g *b.i.d* was used as comparator. The co-primary composite endpoints were efficacy failure (biopsy-proven acute rejection, graft loss, death or loss to follow-up) at 6 months, and graft loss, death or loss to follow-up at 12 months. Certican was, overall, non-inferior to MMF in these trials. The incidence of biopsy-proven acute rejection at 6 months in the B201 study was 21.6%, 18.2%, and 23.5% for the Certican 1.5 mg/day, Certican 3 mg/day and MMF groups, respectively. In study B251, the incidences were 17.1%, 20.1%, and 23.5% for the Certican 1.5 mg/day, Certican 3 mg/day and MMF groups, respectively.	*Renal transplantation* Certican in fixed doses of 1.5 mg/day and 3 mg/day, in combination with standard doses of ciclosporin for microemulsion and corticosteroids, was investigated in two Phase III *de novo* renal transplant trials (B201 and B251). Mycophenolate mofetil (MMF) 1 g *b.i.d* was used as comparator. The co-primary composite endpoints were efficacy failure (biopsy-proven acute rejection, graft loss, death or loss to follow-up) at 6 months, and graft loss, death or loss to follow-up at 12 months. Certican was, overall, non-inferior to MMF in these trials. The incidence of biopsy-proven acute rejection at 6 months in the B201 study was 21.6%, 18.2%, and 23.5% for the Certican 1.5 mg/day, Certican 3 mg/day and MMF groups, respectively. In study B251, the incidences were 17.1%, 20.1%, and 23.5% for the Certican 1.5 mg/day, Certican 3 mg/day and MMF groups, respectively.	
…..	…	
Paediatric population There is insufficient data in children and adolescents to recommend the use of Certican in renal transplantation (see section 4.2). In hepatic transplant paediatric patients, Certican should not be used (see section 4.2).	--	
Renal transplantation In paediatric renal allograft recipients (1-18 years of age; n=30), Certican was assessed in a 12-month, multi-center, randomized, open-label trial with two parallel groups (1:1) evaluating the use of Certican in combination with reduced tacrolimus and corticosteroid withdrawal at 6 months post transplantation in comparison to mycophenolate mofetil with standard tacrolimus. The efficacy for Certican with reduced tacrolimus and steroid withdrawal was comparable to mycophenolate mofetil with standard tacrolimus 13.3% (2/15) vs 6.7% (1/15) for the primary efficacy composite failure endpoint of biopsy proven acute rejection, graft loss and death.	…	

There were no deaths or graft losses. Extrapolation from Certican adult kidney transplant data to Certican paediatric study data and literature showed that the primary efficacy composite endpoint was lower than that observed in adults. Renal function calculated by estimated glomerular filtration rate (eGFR) was numerically better with Certican compared to mycophenolate mofetil with standard tacrolimus. The mean difference in eGFR from randomization to 12-months between groups was 7.2 mL/min/1.73m^2. Altogether 6/15 patients in the Certican group vs. 1/15 in the control group were withdrawn from study therapy. Reasons for study drug discontinuation were in the Certican group: 1 aphthous stomatitis, 1 PTLD, 1 increased blood triglycerides, 1 rejection, 1 withdrawal of consent, 1 administrative reason; in the control group:1 increased creatinine/tacrolimus toxicity. This affects the possibility to evaluate efficacy in terms of long-term renal function. Two patients in the Certican group vs. one in the control had a biopsy proven rejection. Hepatic transplantation In paediatric hepatic transplant recipients (month 1-18 years of age; n=25) receiving either a full-size liver allograft or a technically modified liver allograft from a deceased or living donor, Certican with reduced tacrolimus or ciclosporin was evaluated in a 12-month, multi-center, single arm study. Based on this study with extrapolation to adult study data, the efficacy of Certican with reduced tacrolimus or ciclosporin is comparable to that observed in adults for the primary efficacy composite endpoint of treated biopsy-proven acute rejection, graft loss and death (0% vs. 6.7%). The gain in estimated glomerular filtration rate (eGFR) from randomization to 12-monthswas higher in Certican pediatric patients (9.1 mL/min/1.73m2) to that observed in adults treated with Certican (8.50 mL/min/1.73m^2 vs. control (see Table 20)).		

In paediatric hepatic transplant recipients, there was no negative impact in growth or sexual maturation observed, however, compared to adults and published literature, there were higher rates of serious infections, and GI disorders (particularly gastroenteritis, vomiting, diarrhoea, and stomatitis). Incidence rates for post-transplant lymphoproliferative disorder in the group of children under 7 years of age, and notably in EBV negative children under 2 years of age, were higher compared to adults and published literature. Based on the safety data the benefit/risk profile does not support recommendations for use. …..		

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טופס זה מיועד לפרוט ההחמרות בלבד !

ההחמרות המבוקשות		
פרק בעלון	**טקסט נוכחי**	**טקסט חדש**
תחילת העלון	... תרופה זו אינה מיועדת לתינוקות וילדים מתחת לגיל 18. ניסיון מוגבל עם טיפול בסרטיקן בילדים. ...	... תרופה זו אינה מיועדת לתינוקות וילדים לילדים ומתבגרים מתחת לגיל 18. ~~יש ניסיון מוגבל עם טיפול בסרטיקן בילדים.~~ ...
1. למה מיועדת התרופה?	סרטיקן משמש למניעת דחיית שתל במושתלי כליה ולב מבוגרים ובמושתלי כבד. במושתלי כליה ולב יש ליטול סרטיקן בשילוב עם ציקלוספורין במיקרואמולסיה וקורטיקוסטרואידים ובמושתלי כבד יש ליטול סרטיקן בשילוב עם טקרולימוס וקורטיקוסטרואידים. ...	סרטיקן משמש למניעת דחיית שתל במושתלי כליה ולב ומושתלי כבד מבוגרים~~ובמושתלי כבד~~. במושתלי כליה ולב יש ליטול סרטיקן בשילוב עם ציקלוספורין במיקרואמולסיה וקורטיקוסטרואידים ובמושתלי כבד יש ליטול סרטיקן בשילוב עם טקרולימוס וקורטיקוסטרואידים. ...

2. לפני שימוש **בתרופה**	... **ילדים ומתבגרים** תרופה זו אינה מיועדת לתינוקות וילדים מתחת לגיל 18. יש ניסיון מוגבל עם טיפול בסרטיקן בילדים. ...	... **ילדים ומתבגרים (מתחת לגיל 18)** תרופה זו אינה ~~מיועדת~~ מומלצת לשימוש בילדים ומתבגרים מושתלי כליה~~לתינוקות וילדים~~ מתחת לגיל 18 מאחר ואין מספיק נסיון בטיפול בסרטיקן במטופלים אלו. אין להשתמש בסרטיקו בילדים ומתבגרים מושתלי כבד. ~~יש ניסיון מוגבל עם טיפול בסרטיקן בילדים.~~ ...
4. תופעות לוואי	.... **תופעות לוואי שכיחות (עשויות להשפיע על בין 1 ל- 10 מטופלים בכל 100 מטופלים):** הרעלת דם ; זיהום פצעים ; גידולים סרטניים ושפירים ; סרטן עור ; נזק כלייתי עם רמות נמוכות של טסיות ותאי דם אדומים בדם עם או ללא פריחה ; הרס תאי דם אדומים ; כאב בפה או בגרון ; אקנה ; היווצרות קרישי דם בכלי הדם של הכליה שיכולים לגרום לאובדן השתל בעיקר בפרק הזמן של 30 הימים הראשונים אחרי השתלת הכליה ; הפרעה בקרישת הדם ; רמה נמוכה של טסיות ותאי דם אדומים בדם ; דופק מהיר ; דימומים מהאף ; ירידה במספר תאי הדם (הסימפטומים עשויים לכלול חולשה, חבלות וזיהומים תכופים) ; ציסטות המכילות נוזל לימפטי ; סרפדת (אורטיקריה) ותגובות אלרגיות נוספות כגון התנפחות של הפנים או הגרון (אנגיואדמה), פריחה ; דלקת בלבלב ; כיבים בפה ; כאבי מפרקים ; כאבי שרירים ; חלבון בשתן ; הפרעות כליתיות ; אין-אונות ; בקע (הרניה) באזור הניתוח ; תוצאות לא תקינות של בדיקות כבד. **תופעות לוואי לא שכיחות (עשויות להשפיע על בין 1 ל- 10 מטופלים בכל 1,000 מטופלים):** גידול סרטני של הרקמה הלימפטית (לימפומה) ; רמות נמוכות של טסטוסטרון ; דלקת ריאות ; דלקת של הכבד ; צהבת.	.... **תופעות לוואי שכיחות (עשויות להשפיע על בין 1 ל- 10 מטופלים בכל 100 מטופלים):** הרעלת דם ; זיהום פצעים ; גידולים סרטניים ושפירים ; סרטן עור ; נזק כלייתי עם רמות נמוכות של טסיות ותאי דם אדומים בדם עם או ללא פריחה ; הרס תאי דם אדומים ; כאב בפה או בגרון ; אקנה ; היווצרות קרישי דם בכלי הדם של הכליה שיכולים לגרום לאובדן השתל בעיקר בפרק הזמן של 30 הימים הראשונים אחרי השתלת הכליה ; הפרעה בקרישת הדם ; רמה נמוכה של טסיות ותאי דם אדומים בדם ; דופק מהיר ; דימומים מהאף ; ירידה במספר תאי הדם (הסימפטומים עשויים לכלול חולשה, חבלות וזיהומים תכופים) ; ציסטות המכילות נוזל לימפטי ; סרפדת (אורטיקריה) ותגובות אלרגיות נוספות כגון התנפחות של הפנים או הגרון (אנגיואדמה), פריחה ; דלקת בלבלב ; כיבים בפה ; כאבי מפרקים ; כאבי שרירים ; חלבון בשתן ; הפרעות כליתיות ; אין-אונות ; בקע (הרניה) באזור הניתוח ; תוצאות לא תקינות של בדיקות כבד ; הפרעות במחזור הווסת החודשי (כולל היעדרות של המחזור או מחזור עם דימום כבד). **תופעות לוואי לא שכיחות (עשויות להשפיע על בין 1 ל- 10 מטופלים בכל 1,000 מטופלים):** גידול סרטני של הרקמה הלימפטית (לימפומה) ; רמות נמוכות של טסטוסטרון ; דלקת ריאות ; דלקת של הכבד ; צהבת ; ציסטות בשחלה. ....

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