EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

15 November 2012
EMA/594074/2014
Committee for Medicinal Products for Human Use (CHMP)

Altargo

(retapamulin)

Procedure No. EMEA/H/C/000757/P46/017

CHMP assessment report for paediatric use studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature delete

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ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Altargo Topical ointment 1%
INN (or common name) of the active substance(s):	Retapamulin
MAH:	Glaxo Group Ltd
Currently approved Indication(s)	Altargo is indicated for the short term treatment of the following superficial skin infections in subjects above 9 months of age: Impetigo Infected small lacerations, abrasions or sutured wounds
Pharmaco-therapeutic group (ATC Code):	Antibiotics and chemotherapeutics for dermatological use, Antibiotics for topical use. ATC code: D06AX13
Pharmaceutical form(s) and strength(s):	Topical ointment 1%

1. INTRODUCTION

GSK has submitted to the EMEA the final clinical study report for "A Randomized, Double-Blind, Double Dummy, Comparative,Multicenter Study to Assess the Safety and Efficacy of Topical Retapamulin Ointment, 1%, versus Oral Linezolid in the treatment of Secondarily-Infected Traumatic Lesions and Impetigo Due to Methicillin-Resistant *Staphylococcus aureus"* TOC 110978, which includs paediatric subjects, in accordance with Article 46 of Regulation (EC) No 1901/2006.

GSK states that study TOC110978 is part of a clinical development program, although it is not part of an agreed paediatric investigation plan. Two other studies TOC106489 and TOC110977, which included paediatric subjects, were submitted following the MA approval as eCTD sequences 0026 and 0059 respectively.

A brief expert overview has been provided, which confirms that the data submitted does not influence the benefit-risk balance for Altargo 10mg/g ointment and therefore does not require further regulatory action for the marketing authorisation for Altargo 10mg/g ointment.

No changes to the Altargo SmPC are suggested.

2. SCIENTIFIC DISCUSSION

Information on the pharmaceutical formulation used in the study(ies)

The same formulation (topical ointment) as the currently marketed product has been used in the clinical study.

Clinical aspects

2.1. Introduction

Altargo (retapamulin) is indicated for the short term treatment of the following superficial skin infections in patients above 9 months of age:

- Impetigo.
- Infected small lacerations, abrasions, or sutured wounds.

Retapamulin is a semi-synthetic derivative of the compound pleuromutilin, which is isolated through fermentation from Clitopilus passeckerianus (formerly Pleurotus passeckerianus).

Retapamulin selectively inhibits bacterial protein synthesis by interacting at a unique site on the 50S subunit of the bacterial ribosome that is distinct from the binding sites of other non-pleuromutilin antibacterial agents that interact with the ribosome.

Retapamulin is predominantly bacteriostatic against S. aureus and S. pyogenes.

The Applicant has provided the study report of a phase 3 study "A Randomized, Double-Blind, Double dummy, Comparative, Multicenter Study to Assess the Safety and Efficacy of Topical Retapamulin Ointment, 1%, versus Oral Linezolid in the Treatment of Secondarily-Infected Traumatic Lesions and Impetigo Due to Methicillin-Resistant Staphylococcus aureus". This included children over 9 months.

Previously the applicant has submitted the results of 6 phase 3 randomised studies and one open-label study, which included paediatric subjects. These have been assessed previously.

As this study has been submitted as part of Art 46, this report will concentrate on the findings in the paediatric subjects only.

The MAH submitted a final report for: Study TOC110978.

2.2. Clinical study

Title

A Randomized, Double-Blind, Double Dummy, Comparative, Multicenter Study to Assess the Safety and Efficacy of Topical Retapamulin Ointment, 1%, versus Oral Linezolid in the Treatment of Secondarily-Infected Traumatic Lesions and Impetigo Due to Methicillin-Resistant *Staphylococcus aureus.*

Study

GSK sponsored this study, which was conducted in compliance with GCP. The study commenced on 27 Apr 2009 and ended on 27 Sept 2010. The final study report is dated November 2011.

Objectives: The primary objective of this study was to evaluate the clinical and bacteriological efficacy of topical retapamulin ointment, 1%, versus oral linezolid (Zyvox®), in the treatment of subjects with secondarily-infected traumatic lesions (SITL, excluding abscesses) or impetigo due to methicillin-resistant *Staphylococcus aureus* (MRSA).

There were 2 secondary objectives: 1) to evaluate the safety of topical retapamulin ointment, 1%, versus linezolid, in the treatment of subjects with SITL (excluding abscesses) or impetigo due to MRSA, and 2) to evaluate the efficacy and safety of topical retapamulin ointment, 1%, versus linezolid, in the treatment of subjects with SITL (excluding abscesses) or impetigo, without regard to baseline pathogen.

Methodology: This was a randomized, double-blind, double dummy, multicenter, comparative study in subjects ≥ 2 months of age and older with SITL (including secondarily-infected lacerations, sutured wounds and abrasions) or impetigo (bullous and non-bullous) due to MRSA. Subjects were randomized to either topical retapamulin arm or oral linezolid arm under a 2:1 randomization ratio. Retapamulin was applied twice daily for 5 days, and linezolid was dosed, depending on subject age, either twice or three times daily for 10 days.

Subjects attended up to 5 study visits over a 17 to 19 day period. It was estimated that up to 500 subjects would need to be randomized to obtain 105 subjects that had MRSA as their baseline pathogen. It was expected that there would be approximately 70 subjects with baseline MRSA in the retapamulin arm and 35 in the linezolid arm.

Number of subjects: Proposed – 500, Actual – 410 (270 in retapamulin arm, 140 in the linezolid arm).

Diagnosis and main criteria for inclusion:

1. The subject was aged 2 months or older.

2. The subject had a SITL or impetigo (bullous or non-bullous).

3. The subject had a negative urine pregnancy test prior to enrollment (if of childbearing potential).

4. The subject had a total Skin Infection Rating Scale (SIRS) Score of at least 8, which had to include a pus/exudate score of at least 3.

5. The subject and/or parent/legal guardian was willing and able to comply with the study protocol.

6. The subject or parent/legal guardian, as applicable, had given written informed, dated consent; and the subject had given written assent, if applicable, to participate in the study.

Treatment administration:

Retapamulin or placebo ointment was to have been applied twice daily for 5 days. The ointment formulation should have been applied to the infected lesion(s) at a dose of approximately 10 mg per cm2. Based on the maximum total area of infected lesion(s) to be treated being 100 cm2, the maximum amount of ointment/placebo applied would have been 1 gram (a "jelly-bean" size portion).

Subjects receiving linezolid were to have been dosed, according to age, as presented in the following table:

Linezolid Dosing Information

Age Group	Formulation	Dose
Adolescent and Adult (≥12 years of age)	600 mg tablet	600 mg q12h for 10 days
Pediatric (5 – 11 years of age)	100 mg/5 mL oral suspension	10 mg/kg q12h for 10 days
Pediatric (<5 years of age)	100 mg/5 mL oral suspension	10 mg/kg q8h for 10 days

Criteria for evaluation: Efficacy criteria included measurement of infected wound/lesion, skin infection rating scale, bacteriology of wound/lesion sample, and anterior nares bacteriology.

The *primary efficacy endpoint* was the clinical response at follow-up (7 to 9 days posttherapy; Day 12 to 14 for retapamulin and Day 17 to 19 for linezolid) in subjects with MRSA as the baseline pathogen.

Secondary efficacy endpoints included the following:

- Microbiological response at follow-up in subjects with MRSA as the baseline pathogen.
- Clinical response at follow-up in all subjects.
- Microbiological response at follow-up in all subjects with a baseline pathogen.
- Clinical outcome at end of therapy (2 to 4 days post-therapy; Day 7 to 9 for retapamulin and Day 12 to14 for linezolid) in subjects with MRSA as the baseline pathogen.
- Microbiological outcome at end of therapy in subjects with MRSA as the baseline pathogen.
- Clinical outcome at end of therapy in all subjects.

- Microbiological outcome at end of therapy in all subjects with a baseline pathogen.
- Therapeutic response (combined clinical and microbiological response) at follow-up.

Other endpoints included the following:

- Comparison of percent decrease in wound size from baseline (Day 1) to followup.
- Comparison of SIRS scores from baseline to follow-up
- Descriptive analysis (number and percent) of primary and secondary endpoints,

as defined above, in the pediatric subpopulation

Safety criteria included concomitant medications, adverse events, and serious adverse events. A clinical evaluation and clinical outcome determinations were also performed.

Statistical methods: Six analysis populations were described in this study –

Intent to Treat Clinical (ITTC): All randomized subjects who took at least one dose of study medication.

Intent to Treat Bacteriology (ITTB): All randomized subjects who took at least one dose of study medication and who had a pathogen isolated at baseline.

Intent to Treat MRSA (ITTMRSA): All randomized subjects who took at least one dose of study medication and who had an MRSA isolated at baseline.

Per Protocol Clinical (PPC): Subjects from the ITTC population who adhered to the protocol (did not violate the protocol).

Per Protocol Bacteriology (PPB): Subjects from the ITTB population who adhered to the protocol (did not violate the protocol).

Per Protocol MRSA (PPMRSA): Subjects from the ITTMRSA population who adhered to the protocol (did not violate the protocol).

Because no power calculations were used for sample size considerations, no formal testing of hypotheses was performed for the primary comparison of interest, instead, 95% confidence intervals (CIs) for the difference in the clinical success rates between the 2 treatment groups were calculated. For other comparisons of interest, the number and percent success rate for each treatment in each analysis population was to be presented. The 95% CIs of the difference in success rates between the treatment groups were to be constructed. Clinical response and microbiological response at follow-up by subgroup factors such as demographic characteristics and diagnosis of skin infection at baseline were to be presented.

Determining Clinical Outcome and Response

The clinical outcome at end of therapy was defined as below:

Defining criteria	Clinical Outcome at End of Therapy (Day 7-9, Day 12-14)
Resolution of clinically meaningful signs and symptoms of infection recorded at baseline, including a pus/exudate SIRS score of "0".	Clinical Success
Improvement of signs and symptoms of infection recorded at baseline to such an extent that no further antimicrobial therapy is necessary.	Clinical Improvement
Insufficient improvement or deterioration of signs and symptoms of the infection recorded at baseline, such that additional antibiotic therapy is required. Subjects who are a 'Clinical Failure' at end of therapy are considered a 'Clinical Failure' at follow-up as well.	Clinical Failure
Refusal to consent to a clinical examination, lost to follow-up. Subjects who are 'Unable to Determine' at end of therapy are considered 'Unable to Determine' at follow-up as well.	Unable to Determine

The clinical outcome at end of study was defined as clinical success for those in the first category in the above table, the rest were defined as clinical failures.

Results

Paediatric subject disposition

Table 6.11
Summary of Age Group

		Retapamulin			Linezolid		
Population	Age Groups	N	n	%	N	n	%
ITTC	2 m - <9 m	267	1	0.4%	137	0	0.0%
	9 m - <5 yrs	267	24	9.0%	137	15	10.9%
	5 - <12 yrs	267	28	10.5%	137	14	10.2%
	12 - <18 yrs	267	25	9.4%	137	13	9.5%
	18 - <65 yrs	267	171	64.0%	137	85	62.0%
	>=65 yrs	267	18	6.7%	137	10	7.3%
PPC	2 m - <9 m	235	1	0.4%	112	0	0.0%
	9 m - <5 yrs	235	19	8.1%	112	10	8.9%
	5 - <12 yrs	235	24	10.2%	112	11	9.8%
	12 - <18 yrs	235	24	10.2%	112	11	9.8%
	18 - <65 yrs	235	151	64.3%	112	75	67.0%
	>=65 yrs	235	16	6.8%	112	5	4.5%
ITTB	2 m - <9 m	176	1	0.6%	79	0	0.0%
	9 m - <5 yrs	176	18	10.2%	79	12	15.2%
	5 - <12 yrs	176	17	9.7%	79	10	12.7%
	12 - <18 yrs	176	15	8.5%	79	7	8.9%
	18 - <65 yrs	176	120	68.2%	79	45	57.0%
	>=65 yrs	176	5	2.8%	79	5	6.3%
PPB	2 m - <9 m	152	1	0.7%	65	0	0.0%
	9 m - <5 yrs	152	13	8.6%	65	9	13.8%
	5 - <12 yrs	152	14	9.2%	65	8	12.3%
	12 - <18 yrs	152	15	9.9%	65	6	9.2%
	18 - <65 yrs	152	105	69.1%	65	39	60.0%
	>=65 yrs	152	4	2.6%	65	3	4.6%
ITTMRSA	2 m - <9 m	72	0	0.0%	38	0	0.0%
	9 m - <5 yrs	72	8	11.1%	38	8	21.1%
	5 - <12 yrs	72	7	9.7%	38	3	7.9%
	12 - <18 yrs	72	3	4.2%	38	1	2.6%
	18 - <65 yrs	72	51	70.8%	38	24	63.2%
	>=65 yrs	72	3	4.2%	38	2	5.3%
PPMRSA	2 m - <9 m	61	0	0.0%	32	0	0.0%
	9 m - <5 yrs	61	7	11.5%	32	6	18.8%
	5 - <12 yrs	61	4	6.6%	32	3	9.4%
	12 - <18 yrs	61	3	4.9%	32	1	3.1%
	18 - <65 yrs	61	44	72.1%	32	21	65.6%
	>=65 yrs	61	3	4.9%	32	1	3.1%

Assessor's comments

The number of subjects between 2-9 months was <0.5% in most cases while the number of subjects in each of the other categories was approximately 10% for all the different populations.

Primary Efficacy Endpoint

The comparison of primary interest in this study was the clinical success rate at follow-up (7 to 9 days post-therapy, which was Days 12 to 14 for retapamulin and Days 17 to 19 for linezolid) in subjects with MRSA as the baseline pathogen. Clinical success was defined as resolution of clinically meaningful signs and symptoms of infection recorded at Baseline, including a pus/exudate SIRS score of '0.' For subjects in the PP population with baseline MRSA, the success rate in retapamulin-treated subjects was significantly lower than in the linezolid-treated subjects.

An analysis was performed using a definition of clinical success as both clinical success and clinical improvement (defined as improvement of signs and symptoms of the infection recorded at baseline) at follow-up. Because there were approximately 2-fold the number of subjects in the retapamulin group who were considered to have improved vs subjects in the linezolid group, adding subjects with clinical improvement increased the success rate in PPMRSA retapamulin-treated subjects to 91.8% and to 100% in the linezolid group. The difference was not considered to be significant.

When subgroup factors are considered, tests for association between factors and possible significant effect on clinical response were restricted to compliance in the ITTC and ITTMRSA populations. When the clinical response in pediatric subjects (<18 years of age) and adults (≥18 years) were compared, it appears that significant differences between retapamulin and linezolid occurred in adult subjects with SITL in all but the ITTMRSA populations. There were no apparent differences in pediatric response rates when comparing 95% CI for SITL or impetigo.

Clinical Response at Follow-up by Subgroup Factors (ITTC)

Subgroup	Retapamulin Successes/N	Retapamulin Success Rate	Linezolid Successes/N	Linezolid Success Rate	Difference in Success Rates [1]
Age					
2 m - <9 m	1/ 1	0.0%	0/ 0		
9 m - <5 yrs	18/ 24	75.0%	12/ 15	80.0%	-5.0%
5 - <12 yrs	22/ 28	78.6%	12/ 14	85.7%	-7.1%
12 - <18 yrs	21/ 26	80.8%	11/ 12	91.7%	-10.9%
18 - <65 yrs	90/171	52.6%	73/ 85	85.9%	-33.3%
>=65 yrs	10/ 18	55.6%	4/ 10	40.0%	15.6%

Assessor's comments

The clinical success rates are not very different between the two groups, at least in the paediatric subjects.

Skin Infection (Rating Scale)

All subjects in the ITTC and PPC populations had measurable exudate/pus at Visit 1. By Visit 3 for both treatment groups and in both the ITTC and PPC populations the median SIRS score for exudate/pus was 0.0. The proportion of subjects with a '0' score decreased similarly in the retapamulin and linezolid groups for both analysis populations, by Visit 5 <3% of subjects had any measurable exudate/pus.

Mean SIRS scores were comparable in the retapamulin and linezolid treatment groups and in the ITTC and PPC populations at Visits 1 and 2. By Visit 3, the mean SIRS score was slightly lower and with a lower standard deviation (SD) in the linezolid treatment groups, indicating that subjects in the linezolid

treatment group had a more predictable response to treatment after Visit 2. Total median SIRS scores for the retapamulin and linezolid groups were nearly identical in the ITTC and PPC populations. The median total SIRS score was 19 at Visit 1, decreasing rapidly to 3 at Visit 3. By Visit 5, the median score was '0' for all treatment groups and analysis populations.

Microbiological Response

Microbiological success rates at follow-up in the retapamulin group were significantly (approximately 27%) lower than the linezolid group; for both treatment groups the PP populations had approximately 6% better microbiological success rates than the corresponding ITT populations. Results of a therapeutic response evaluation, where therapeutic success is defined to be clinical and microbiological successes, indicate that the number of subjects who achieve therapeutic success is the same as the number of subjects achieving microbiological success (therefore microbiological success is the limiting factor in achieving therapeutic response). The response rate (considered to be presumed eradication) at follow-up in non-*S. pyogenes* streptococcal species was about the same for retapamulin and linezolid (approximately 63%); for all other pathogens with a sample size >2, linezolid had an approximately 30% greater pathogen eradication rate than retapamulin. In general, presumed recurrence was the reason for microbiological failure. Study medication compliance (80% to ≤120% vs 'other') significantly affected microbiological success (ITTB and ITTMRSA populations).

Safety

The ITTC population was used for all safety assessments. In total, 78 (16.2%) of subjects in the retapamulin group and 42 (30.7%) of subjects in the linezolid group had reportable adverse events. Adverse events were infrequently reported, with only 3 AEs (diarrhea, nausea, and headache) reported by ≥3% of subjects in either group. Most AEs were reported by 1 subject in either group. Most AEs were considered to be mild or moderate in intensity. In retapamulin-treated subjects, a diagnosis of impetiginous lesion non-bullous appears to result in a higher AE rate (46.9%) compared with other diagnoses, and subjects with a diagnosis of secondarily-infected laceration had a lower incidence (14.6%) of AEs compared with other diagnoses, which were in the 20 to 36% range. Age did not appear to play a factor in the proportion of subjects reporting AEs in the retapamulin group; in the linezolid group a higher proportion of older subjects (over 65) reported AEs.

In general, the AEs considered to be related to treatment are expected for the drug class and route of administration. Linezolid subjects experienced more related gastrointestinal events than retapamulin subjects; retapamulin subjects experienced more related skin and subcutaneous events than linezolid subjects. Only nausea and diarrhea occurred in >5 of subjects in either group.

Overall, 11 (4.1%) and 4 (2.9%) of subjects in the retapamulin and linezolid groups, respectively, withdrew from the study due to adverse events. There were 8 subjects in the retapamulin group that withdrew due to adverse events in the Infections and Infestations system organ class (SOC), no subjects in the linezolid group withdrew due to AEs in this SOC. Of the 11 subjects in the retapamulin group that withdrew due to AEs, only cellulitis (n = 3) was noted more than once. Serious adverse events were rarely reported (n = 6 subjects total). Four subjects had SAEs involving infectious processes, there was 1 musculoskeletal SAE (hip fracture) and 2 metabolic SAEs (hypoglycemia and hyponatremia).

Summary of Adverse Events by Subgroup Factors

Subgroup Factor	Retapamulin (N=267)	Linezolid (N=137)
Age		
2 m - <9 m	1/ 1(100.0%)	0/ 0
9 m - <5 yrs	6/ 24 (25.0%)	3/ 15 (20.0%)
5- <12 yrs	11/ 28 (39.3%)	2/ 14 (14.3%)
12 - <18 yrs	9/ 25 (36.0%)	5/ 13 (38.5%)
18 - <65 yrs	38/171 (22.2%)	27/ 85 (31.8%)
>=65 yrs	5/ 18 (27.8%)	5/ 10 (50.0%)

Assessor's comments

The adverse event profiles are not very different between the two groups, except the 5-12 group, where the AEs in the Retapamulin group are twice the number in the Linezolid group.

Conclusions:

The applicant concluded that Retapamulin had a significantly lower rate of clinical and microbiological response than linezolid although wound size and SIRS scores decreased over time in both treatment groups and to a similar extent by end of treatment.

Topical retapamulin provides a therapeutic alternative to other antibiotics particularly in cases of impetigenous lesions, and can be effective against MRSA although it is more active against MSSA and other susceptible pathogens. Retapamulin was less active against SITA infections than for treatment of impetigenous lesions.

Both retapamulin and linezolid were well tolerated in this study, with a low incidence of AEs and SAEs reported in both treatment groups. However a majority of subjects preferred the topical medication over the oral medication.

2.3. Discussion on clinical aspects

The safety and efficacy of Retapamulin in the adult and paediatric groups is similar. The number of subjects under 9 months was <0.1% and therefore no conclusions in this age group are possible.

It is agreed that the results of this study do not raise any specific concerns in the paediatric population and therefore no further regulatory action is considered necessary.

However it is noted that neither the clinical overview nor the clinical study report concentrated on presenting data in the paediatric population. The expert statement and overview were very inadequate in presenting data in the relevant population and it was extremely difficult to find this information in the submitted documentation.

3. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

Overall conclusion

The results of this study do not raise any specific concerns in the paediatric population and therefore no further regulatory action is considered necessary. However an adequate clinical overview concentrating on the results of the study in the paediatric population should be submitted.

Recommendation

Based on the data submitted, the MAH should provide additional clarifications requested for this study as part of this procedure (see section IV "Additional clarifications requested")

4. ADDITIONAL CLARIFICATIONS REQUESTED

1. Please clarify the reasons for the larger number of adverse events in the 5-12 year group.
2. Please present the data relevant to the paediatric population, particularly the results in a separate document, preferably as part of the clinical overview, which should include the clinical expert's assessment of the study results.

The timetable as proposed by the Rapporteur is as follows:

A 30 day response timetable with clock stop will apply.