

**Public Assessment Report
for paediatric studies submitted in accordance
with Article 45 of Regulation (EC) No1901/2006, as
amended**

**Phenoxyethylpenicillin
Oral formulations**

NO/W/0002/pdWS/001

Marketing Authorisation Holders:

Sanofi Aventis Deutschland GmbH

Sandoz

Infectopharm

MEDA Ltd

Rapporteur:	NORWAY
Finalisation procedure (day 120):	06.05.2010/Updated: 31.05.2010
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ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	Phenoxymethylpenicillin
INN (or common name) of the active substance(s):	Phenoxymethylpenicillin
MAH (s):	Sanofi Aventis Deutschland GmbH Sandoz Infectopharm MEDA Ltd
Pharmaco-therapeutic group (ATC Code):	J01CE02
Pharmaceutical form(s) and strength(s):	Film-coated tablets Soluble tablets Granules for oral suspension Powder for oral solution Oral suspension

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List of abbreviations

AOM	acute otitis media
BID	twice daily
EM	Erythema migrans
ENT	Ear nose and throat
GABHS	group A β -haemolytic streptococci
LB	Lyme borreliosis
MAH	marketing authorisation holder
MIC	minimum inhibitory concentration
PD	Pharmacodynamics
PK	Pharmacokinetics
PL	Package leaflet
QD	once daily
QID	four times daily
SmPC	Summary of product characteristics
TID	three times daily

I. EXECUTIVE SUMMARY

The data from the submitted studies and scientific articles do not specifically suggest any need of major change in the current paediatric information in the SmPC for penicillin V. However, there are a few issues which should be specified in the SmPC.

II. RECOMMENDATION

The following SmPC and PL changes are proposed:

- To cover the possible differences in paediatric use of penicillin V in different member states due to the heterogeneous resistance situation in Europe, the following standard text is proposed to be added to section 4.1 (if it is lacking): “*Consideration should be given to official guidance on the appropriate use of antibacterial agent*”.
- Based on the submitted studies, the following information is proposed to be added in section 4.2 (if it is lacking): *To avoid late complications (rheumatic fever), infections with β -haemolytic streptococci should be treated for 10 days*”.
- If acute otitis media is included in the indication, the following wording should be added in section 4.2: “*The treatment of acute otitis media with penicillin V should be limited to 5 days. However, 5-10 days treatment may be recommended in patients with potential for complications*”.

In addition to the above changes to SmPC and PL, authorisation holders are encouraged to conduct studies to provide information on the use of phenoxymethylpenicillin in the following circumstances:

Concomitant administration with food:

The compliance in children would be better if penicillin V is concomitantly administered with food. Since both recommendations (penicillin V intake with food or 1-2 hours prior to food) are based on outdated data, new and more solid pharmacokinetic data on the interaction between food and phenoxymethylpenicillin is desirable.

Erythema migrans:

Treatment duration varies depending on the stage and severity of infection, and the age of the patient. Treatment of localized skin infections should continue for 14 days; treatment of early disseminated infection, for 21 days; treatment of acrodermatitis (which occurs predominantly in Europe), for 30 days; and treatment of Lyme disease-associated arthritis, for 30 to 60 days (Kasper et al. 2005). However, the necessary duration of antibiotic treatment has not been adequately studied in clinical trials. Therefore, there is need for clinical trials, which make basis for dose recommendation regarding EM.

III. INTRODUCTION

Phenoxymethylpenicillin, commonly known as penicillin V, is narrow spectrum penicillin for oral administration. It is less potent than benzylpenicillin, and appropriate in conditions where

high tissue concentrations are not required. Penicillin V exerts a bactericidal action through the inhibition of biosynthesis of cell-wall. It is primarily effective against aerobic, Gram-positive organisms such as streptococci, enterococci, and some staphylococci that do not produce beta-lactamase. In paediatrics, penicillin V have been primarily used for the treatment of ear, nose and throat infections, lower respiratory tract infections, dental infections, skin and soft tissue infections caused by Group A β -haemolytic streptococci (GABHS), e.g. scarlet fever and erysipelas, and also as prophylaxis against the recurrence of rheumatic fever.

Clinical studies that were not previously evaluated by authorities and/or published scientific articles were received from Infectopharm, Meda, Sandoz and Sanofi Aventis, in accordance with article 45 of the regulation (EC) No 1901/2006 as amended on medicinal products for paediatric use.

An assessment on the currently available data regarding paediatric use of penicillin V was performed in this Article 45 procedure with NO acting as Rapporteur. The issues raised and discussed during this procedure are summarized below in Scientific Discussion.

IV. SCIENTIFIC DISCUSSION

IV.1 Differences in indications and posology in different countries

It has been identified some differences regarding the indications and dose recommendations between the SmPCs for the penicillin V formulations marketed in Norway and the SmPC submitted by the MAH. The precise wording of SmPCs may differ in various member states (MS). It could have been useful to have more information on the paediatric use of penicillin V in different MSs for the purpose of harmonization. However, in the frame of the current procedure, this is a difficult task. The MAHs were encouraged to evaluate the need for harmonization of the paediatric information via other appropriate regulatory procedures.

Response from MAHs:

The MAHs were not in a position to propose a harmonized text in the frame of this procedure, mainly due to specific national recommendations or medical practices regarding the use of antibiotics, including phenoxymethylpenicillin.

Rapporteur's final comments:

In order to cover the possible differences in paediatric use of penicillin V in different member states due to the heterogeneous resistance situation in Europe, the following standard text is proposed to be added to the SmPC section 4.1 (if it is lacking): "Consideration should be given to official guidance on the appropriate use of antibacterial agent". This proposal was endorsed by the MAHs.

IV.2 Clinical aspects regarding posology and administration

IV.2.1 Duration of treatment in the treatment of streptococcal pharyngitis/tonsillitis

Based on the submitted studies, the following information is proposed to be included in the SmPC section 4.2 (if it is lacking): “To avoid late complications (rheumatic fever, glomerulonephritis), infections with β -haemolytic streptococci should be treated for at least 10 days”.

Rapporteur’s final comments

After input from other member states the above recommendation has been amended to: “To avoid late complications (rheumatic fever), infections with β -haemolytic streptococci should be treated for 10 days”.

IV.2.2 Duration of treatment in the treatment of acute otitis media:

Based on the submitted studies, the following information is proposed to be included in the SmPC section 4.2 (if it is lacking): “The treatment of acute otitis media with penicillin V should be limited to 5 days”.

However, MAHs regarded the clinical evidence for the restriction to 5 days to be insufficient.

Response from MAH 1:

The applicant disagrees with the recommendation to limit the treatment duration in acute otitis media to a maximum of 5 days. Clinical evidence for this recommendation is regarded to be insufficient. Due to the high rate of spontaneous clinical cure, which is correctly mentioned by the Rapporteur, trials comparing different treatment regimens simply on the basis of clinical success would require very high patient numbers to verify or disprove equivalence between antibiotic regimens. This results in a situation in which regimens with poor antibacterial activity may seem to be effective when they are not. It is widely acknowledged that a reliable way to make a comparative judgement on efficacy based on a reasonable study size is the so called “double tympanocentesis” approach. By means of two tympanocentesis and cultures prior to and during or shortly after completion of treatment, the bacteriological cure rate can be determined.

To our knowledge there is no evidence from either sufficiently powered trials with clinical endpoints or from “double tympanocentesis” trials to recommend a rather short treatment duration of 5 days in otitis media.

Response from MAH 2:

We disagree with the recommendation to use penicillin V in the treatment of acute otitis media with restricted therapy duration of 5 days. This recommendation does not appear to be justified by internationally acknowledged evidence-based data. It should in particular be noted that penicillin V is not considered as first line therapy for AOM in many non Nordics countries, and that there is therefore no consensus on the therapy of AOM, as the Rapporteur correctly mentions in the Assessment Report. We question therefore the value of issuing such a recommendation that will not be applicable to many EU countries.

Rapporteur’s final comments:

We agree that a reliable way to make a comparative judgement on efficacy based on a reasonable study size is the so called “double tympanocentesis” approach. To the best of our knowledge, it is not clear whether the “double tympanocentesis” approach has been performed for a short treatment of 5 days in acute otitis media. The treatment of acute otitis

media for 10 days is also not based on results from a “double tympanocentesis” approach with phenoxymethylpenicillin as a drug of choice. However, otitis media is a self-limiting disease, which resolves spontaneously in 80% of the cases without antibiotic treatment. The causative agent may be viruses, or the disease may be due to inflammation in the middle-ear. Spontaneous eradication in acute otitis media has also been observed, although the causative agents are bacteria. Howie & Ploussard observed spontaneous eradication rates of 18% for *Streptococcus pneumonia* and 48% for *H. influenza* (Howie & Ploussard 1972).

Shortening the treatment duration would reduce overuse of penicillin V in diseases which are actually known for a high spontaneous cure rate. This would result in less development of resistance in both pathogenic as well as non-pathogenic bacteria in patients. However, 5-10 days treatment may be recommended in patients with potential for complications.

IV.2.3 Dosing frequency

It was identified differences in dosing frequency of penicillin V. In some clinical studies a twice daily dosing regimen was used while a 3-4 times daily regimen was used in the majority of the published studies. In addition, a twice daily dosing is recommended for the ENT infections in the SmPC submitted by Sanofi Aventis. Serum half-life of penicillin V is about 30-45 minutes. Considering that $T > MIC$ is the PK/PD index that correlates best with the efficacy of betalactam antibiotics, it seems quite unlikely to reach adequate serum concentrations with a twice daily dosing of penicillin V. Suboptimal concentrations of an antibacterial agent are known to cause resistance development. The MAHs was asked to comment on this issue, and provide a PK/PD analysis with regards to different indications to substantiate the optimal dosing frequency of penicillin V.

Response from MAH 1:

It is widely acknowledged that the percentage of time above minimal inhibitory concentration ($\%T > MIC$) is the appropriate PK/PD parameter for determining dosage intervals for beta-lactam antibiotics such as phenoxymethylpenicillin, with a coverage of 40% of the dosage interval as an accepted lower limit (Jacobs, 2003). The MAH also refers to the PK/PD study submitted by one of the other MAHs and described below, concluding that the PK/PD criterion of 40% $T > MIC$ is fulfilled for the treatment of GABHS infections when the total daily dose is divided into 2 single doses 12 hours apart.

Furthermore, of even greater importance, data from clinical trials also clearly support the twice-daily dosing regimen for the treatment of tonsillopharyngitis by GABHS (Lennon et al., 2009; Raz et al., 1995; Lan and Colford 2000; Bass et al., 2000; Red book 2006; German SmPC template). Therapeutic goal for the antibiotic treatment in patients with GABHS infection is the eradication of the pathogen, in order to prevent suppurative and systemic non-suppurative complications such as abscesses on the one hand and acute rheumatic fever on the other hand. Thus, dosage regimens must be proven to be efficacious in GABHS eradication.

Response from MAH 2:

The MAH has submitted a comparison of the approved BID dosage regimens approved in some EU countries, i.e. AT, DE and FR.

It is generally acknowledged that for beta-lactams, a time above MIC ($T > MIC$) of at least 40% of the dosage interval is the critical parameter correlated to efficacy. Recent

developments of new beta-lactam formulations such as Augmentin XR (16:1 ratio) have been based on the rationale to provide coverage of at least 40% of dosage interval for the respective target pathogen (e.g. penicillin-resistant *S. pneumoniae*) (EC Annex I-III, EMEA/CHMP/97898/2009).

The MAH submitted an exploratory PK/PD study (DV 1/99), evaluating the T>MIC with various Penicillin V dosage regimen, in order to confirm on a PK/PD level the adequacy of the BID dosage to be used in the clinical trial. As this study was performed in healthy adult volunteers, it was however not submitted in the framework of this Article 45 Pediatric Worksharing procedure. The main study report is now provided, together with an additional recalculation, with the present response document. The study evaluated the respective T>MIC for MIC values of 0.03 and 0.06 mg/l, based on the findings reported by Baquero et al. (1999), with MIC90 values of < 0.015 for 786 strains of *S. pyogenes*. The reported upper range was 0.06, value which was therefore considered as the worst case analysis. A similar MIC90 value of < 0.015 was reported from Spain in 2001 by Perez-Trallero et al. (2001) on 2039 strains of *S. pyogenes*. As a more recent USA survey on 4508 strains of *S. pyogenes* reported a MIC90 value of < 0.06 with a range of 0.06 – 0.12 (Brown et al. 2004), an additional recalculation of the study data for MIC values of 0.12 as worst case analysis was performed.

The MAH concludes that the results of study DV 1/99 show that the BID dosage regimen achieves more than 49% of dosage interval coverage for the worst case MIC values of 0.06, whereas for susceptible *S. pyogenes* strains with an expected MIC90 of 0.015, the concentrations exceed the MIC for 57.8% of the 12-hourly dosage interval. The additional worst case analysis performed for MIC values of 0.12 µg/ml still supports the BID dosage regimen, since 46.03% of dosage interval is covered. Since no penicillin resistance has been described to date for the causative pathogen *S. pyogenes*, these results fully support the PK/PD rationale of a twice daily administration of penicillin V in the indication tonsillitis.

Response from MAH 3:

Pharmacokinetics/Pharmacodynamics describes the dose, concentration and response relationships, integrating the dosage regimen and the PK of the antibiotic with the susceptibility of the causative pathogen (MIC). For β Lactam there is a direct relation between Time > MIC and efficacy (Levison et al., 2009) which favours a 3-4 times daily dosing. Penicillin V is approved for ENT infections, such as pharyngitis, tonsillitis, laryngitis, sinusitis, otitis media. Of these, “group A streptococcal pharyngitis” is best described in national recommendations and in the literature. Group A streptococcal pharyngitis is the only ENT- indication for which sufficient data on different dosage regimens are available for a comparison.

Guidelines analysis

National guidelines for the treatment of group A streptococcal pharyngitis with penicillin V in children recommend a BID or TID dose interval.

The different recommended dosing frequencies for children are summarized in Table 1.

Table 1: Recommended dosing frequencies for the treatment of group A streptococcal pharyngitis in children, according to national guidelines

PEG-recommendation (Germany - 2006) (Lode et al. 2006)	IDSA guideline 2002 (Bisno et al 20002)	American Heart Association 2009 (Greber et al. 2009)
100 000 IU/kg/day (59 mg/kg/day) max 2 mio. IU divided in 2 doses	250 mg BID* or TID*	Children (\leq 27 kg): 250 mg BID [#] or TID [#] Children (> 27 kg): 500 mg BID or TID [#]

*This recommendation is based on good evidence and the evidence was sourced from 1 or more well-designed clinical trials without randomization.

[#] Class I, LOE B: Conditions for which there is evidence and/or general agreement that a given procedure or treatment is beneficial, useful, and effective (Class I), data derived from a single randomized trial or nonrandomized studies (LOE B).

Comparison of studies concerning different dosing frequencies

The designs and results of randomized clinical trials is summarised in Table 2, regarding efficacy of different dosing frequencies of penicillin V for 10 days in the treatment of streptococcal pharyngitis.

Table 2: Cure rates (bacteriological eradication) with penicillin V as test drug in patients with group A β -hemolytic streptococcal pharyngitis as determined by throat swab cultures

Study	N	Age (years)	Dosage	Durati on of treatm ent	Test	Cure rate (Bacteriologi cal eradication)
Krober 1990	48	3-18	- 1000 mg QD	10 days	Throat culture	69 %
	48		- 500 mg BID			94 %
	46		- 250 mg QID			89 %
Gerber 1985	49	2-16	- 250 mg BID	10 days	Throat culture	71.5%
	50		- 250 mg TID			82 %
Pichichero 1999	183	2-21	- 500 mg BID	10 days	Throat culture	71.6 %
	176		- 250 mg TID			71.6 %
Spitzer 1977	173	2-56	- 500 mg BID	10 days	Throat culture	83 % [#]
	154		- 250 mg TID			84 % [#]
Fyllingen 1991	100	\geq 5	- 2 Mio (5-11 y.) (= 1180 mg) - 4 Mio (> 11 y.) (= 2360 mg) divided in two doses	7 days*	Throat culture	86 %
	102		- 2 Mio (5-11 y.)			

			(= 1320 mg) - 4 Mio (> 11 y.) (=2640 mg) divided in three doses			90.2 %
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N = number of evaluated patients

throat cultures yielding fewer than ten colonies and less than 30 % of all colonies of the target organism were considered to be negative.

* duration of treatment was less than 10 days.

The results of these studies showed that BID dosing is as effective as more frequent dosing regimens (TID or QID) in the treatment of streptococcal pharyngitis based on the bacteriological success rate (throat culture).

Comparison of studies with penicillin V (BID or TID) as comparator

A 10-day schedule of oral penicillin is the recommended first-line agent in the treatment for streptococcal pharyngitis. Therefore, penicillin V is often used as a well-established comparator to other antibiotics in clinical studies for the treatment of streptococcal pharyngitis.

In the following randomized studies (see Table 3) penicillin V was used as a comparator and was administered to the patients either twice or three times daily (studies with similar age range and test method were compared).

Table 3: Cure rates (bacteriological eradication) with penicillin V as comparator in patients with group A β -hemolytic streptococcal pharyngitis as determined by throat swab cultures

Study	N	Age (years)	Dosage*	Duration of treatment	Test	Cure rate (Bacteriological eradication)
Lennon, 2008	159	5-12	500 mg (250 mg \leq 20 kg) BID	10 days	Throat culture	86.2 %
Gooch, 1993	126	2-13	16.7 mg/kg TID (max 750 mg)	10 days	Throat culture	77.0 %
Cohen, 2002	146	2-12	15 mg /kg TID	10 days	Throat culture	84.2 %
Adam, 2000	1422	1-18	50 000 IU/kg/day (29.5 mg/kg/day [#]) divided in 3 doses (max 750 mg)	10 days	Throat culture	84.1%
Cohen, 1996	136	3-15	15 mg/kg TID	10 days	Throat culture	85.3 %
Dajani, 1993	138	1.5-18	13.4 mg/kg TID	10 days	Throat culture	81.2 %
Still, 1993	199	0.5-12	13.3 mg/kg TID	10 days	Throat culture	81 %

Table 3 cont.: Cure rates (bacteriological eradication) with penicillin V as comparator in patients with group A β -hemolytic streptococcal pharyngitis as determined by throat swab cultures

Study	N	Age (years)	Dosage*	Duration of treatment	Test	Cure rate (bacteriological eradication)
Pichichero, 1995	125	3-18	25 mg/kg/day divided in 3 doses	10 days	Throat culture	80 %
McCarty, 2000	244	0.5-12	13.3 mg/kg TID (max 1.5 g /day)	10 days	Throat culture	78 %
Schaad, 2001	130	2-12	100 000 IU/kg/day (= 59 mg/kg/day) divided in 3 doses	10 days	Throat culture	81 %
Syrogianopoulos, 2004	135	2-16	30 mg/kg/day divided in 3 doses	10 days	Throat culture	84 %

N= number of evaluated patients

*recalculated as amount per dose

The relationship between units and weight is as follows:

1 mg of phenoxymethylpenicillin (free acid) is equivalent to 1695 units

A comparison of the cure rates based on bacteriological eradication obtained with penicillin V in these studies showed that the efficacy of BID and TID is the same. Thus, for twice daily treatment, an efficacy of 86.2 % was obtained, whereas for three times daily treatment a similar, but slightly lower efficacy of 77 % - 85.3 % was observed.

Rapporteur's final comments:

One of the MAHs refers to the review article of Jacobs (2003). The review paper refers to the work published by DuBose et al. 1998, a randomized study for treatment of children with otitis media, with antibacterial agents like azithromycin, cefaclor or amoxicillin (3 times daily, 10 days). First, the paper includes no data indicating that T>MIC was above 40%. Second, the pharmacokinetics for phenoxymethylpenicillin may be different from the antimicrobial agents mentioned above. In addition, the T>MIC value may be different for different bacteria and for different antimicrobial agents (Craig 1996). In this article, it is stated that, a time above MIC greater than 40% was required to achieve a 100% bacteriologic cure rate for bacteria like *S. pneumonia* and *H. influenza*. While T>MIC varied from 50% to 100% for cefaclor, cefuroxime, amoxicillin/clavulanate, cefprozil, loracarbef, cefprozoxime and cefixime against penicillin-susceptible *S. pneumoniae*, it was between 17% and 100% for *H. influenza* and for most other antibacterials <40%.

We are not aware of any data which shows that T>MIC as low as 40% for phenoxymethylpenicillin against *S. pneumonia* and *H. influenza* is sufficient for treatment of these bacteria. The new studies and the meta analysis to assess the impact of dosage frequency on the efficacy of oral penicillin V for the treatment of acute pharyngitis due to GABHS shows that twice-daily dosing was as efficacious as the more frequent dosing regimens, whereas once-daily was inferior. Failure rates with penicillin V therapy have ranged from 5% to 35% for GABHS pharyngitis in various studies (DuBose 2002). One of the reasons for treatment failure may be poor compliance. Several of the studies provided by MAH show better compliance to phenoxymethylpenicillin when prescribed twice-daily rather than 3 or 4 times daily.

The submitted PK/PD study (DV 1/99) was performed in healthy individuals and it is not clear that the PK of phenoxymethylpenicillin is similar in healthy versus patients with infection. Furthermore, the MAH has not discussed the extrapolation of the PK data from adults to children.

The data presented by MAH concerned mean values. It would be desirable if the values were presented with standard deviation (SD), including median and range of the values. Sandoz should inform which method they have used for reanalyzing of data to determine T>MIC-value. The MAH should describe in more detail the reasoning behind the reanalysis. According to the Table1 (above): time above MIC values for MIC limits, 0.015, 0.03, 0,06 and 0,12 for subject nr. 10 the T>MIC-value is < 40% (4.7300: 12= 0.394 or 39.4%) and for subject 6 it is exactly 40%. Although T>MIC=40% might be accepted as cut-off, it would result in therapy failure in many patients. Furthermore, the number of individuals included in the study (n=12) is presumably not sufficient to reflect the inter-individual variation in PK. Thus, there seems to be a potential risk for therapeutic failure in individual patients with the proposed posology.

The MAH concludes that clinical data supporting an alternative twice daily dosing of penicillin V for the treatment of ENT infections are available in the literature only for the indication “streptococcal pharyngitis”. We agree that data regarding twice daily dosing of penicillin V for the treatment of ENT infections are sparse. We do not endorse to incorporate the following statement suggested by one of the MAHs:

For infections of the ear, nose, and throat the daily dose may be given in two single doses – preferably in intervals of 12 hours.

IV.2.4 Compliance problems due to bitter taste of phenoxymethylpenicillin

In almost all studies in which oral penicillin V suspension was used as study medication, the authors commented upon poor compliance due to the bitter taste of penicillin, especially in youngest children. According to the SmPC and general knowledge about penicillin, bioavailability of oral penicillin V is reduced when concomitantly administered with food or milk. However, it has not been found a PK study which fulfils current requirements for clinical studies and which supports the above conclusion. The previous PK studies are outdated, and old microbiological assays were used to measure the serum concentrations. The MAHs should comment on this issue and provide more PK data on food interaction, if there exists any solid or newer studies.

Response from MAH 1:

No own data from PK studies are available to the MAH. A literature review identified 5 pharmacokinetic studies in children (numbers I-V), which were published between 1977 and 1989 which do not add significant evidence. Furthermore we found a recent commentary on this issue from Norway (number VI), wherein, nevertheless, also no newer studies are cited.

We conclude that no PK studies using current methodology to compare serum concentrations in fasting and fed subjects are available.

As a consequence of the known data we recommend to adhere at the actual wording of the SmPCs for the phenoxymethylpenicillin-containing medicinal products of Infectopharm that is also in accordance with the German SmPC template “BfArM-Mustertext”:

“Phenoxymethylpenicillin should be taken about 1 hour before the meals, in order to maximise the absorption rate.

Children may take the medicinal product also during meals in order to facilitate the regular intake.”

Response from MAH 2:

The pharmacokinetic information in the approved SmPC for penicillin V concurs with regard to amount of bioavailability and effect of food on the resorption, as shown in Table 4.

Table 4: Pharmacokinetic information in SmPCs section 5.2

	AT	DE	FR
Bioavailability	Approx. 60%	Approx. 60%	Approx. 55-60%
Resorption reduced by food intake	Yes	yes	Yes
Intake together with milk reduces Cmax	-	-	Yes

No other data are available to the MAH, as no fed bioequivalence/bioavailability studies or food interactions studies were performed by the MAH with penicillin V formulations.

Response from MAH 3:

No new or solid studies are available on the interaction between phenoxymethylpenicillin potassium and food.

The most recent publication (1995) on concomitant administration of penicillin V and food, studied the pharmacokinetics of penicillin V in malnourished and normal weight children. The absorbed dose and the bioavailability were decreased by 14.3 %, from 54.8 % in fasted state to 47.0 % in the non-fasted state after oral administration of penicillin V to non-fasting as compared to fasting normal weight children.

These results are in accordance with the findings of previous publications that absorption, peak concentrations and bioavailability are impaired by simultaneous food intake. The best absorption was observed when phenoxymethylpenicillin potassium was given after at least two hours of fasting, followed by no food intake for one hour.

However, the concomitant intake of a penicillin preparation with food will enhance the compliance and general acceptability by children which may outweigh a possibly reduced bioavailability.

It is very difficult to obtain newer PK data regarding the bioavailability of oral penicillin V when concomitantly administered with food.

The general recommendation that phenoxymethylpenicillin potassium should be taken about one hour before a meal should therefore be maintained in the SmPC as long as no newer information on the interaction of penicillin V with food is available. This recommendation is in line with the current German model SmPC for penicillin V.

However, regarding compliance especially in children, the MAH proposes to replace the current approved sentence in the German Isocillin syrup and Isocillin 1.2 Mega SmPCs by the following: "To facilitate regular ingestion in children, Isocillin syrup/tablets may be taken with a small food intake at least one hour before a meal."

Rapporteur's final comments:

The compliance in children would be better if penicillin V is concomitantly administered with food. However, since both recommendations (intake with food /fasting intake of phenoxymethylpenicillin) are based on outdated data, new and more solid pharmacokinetic data on the interaction between food and drug is desirable.

IV.3 Clinical aspects regarding indications

IV.3.1 Erythema migrans

Regarding the indication “erythema migrans”, two randomised controlled studies with children, confirmed the efficacy and safety of penicillin. In both studies, duration of therapy was longer (14 days) and the doses used were higher than that indicated in the SmPC submitted by the MAH. In previous studies on adults, penicillin V was shown to have good efficacy when used for 10 days. Consequently, it may be considered to add specific information to the SmPC 4.2 that duration of treatment for EM should be 10-14 days. The MAHs was asked to further discuss this issue and make a proposal for a dose recommendation regarding EM.

Response from MAH 1:

Phenoxymethylpenicillin may or may not be approved for the treatment of erythema migrans (EM) in different member states. The approved indications for the phenoxymethylpenicillin-containing medicinal products of Infectopharm do not include the treatment of erythema migrans.

Therefore a provision has to be added in the Assessment report, stating that the above posology information in the section 4.2 should only be added to the SmPC, “if the indication erythema migrans is covered by the marketing authorisation of the respective medicinal product”. This provision is important to avoid discrepancies between sections 4.1 and 4.2.

Response from MAH 2:

It should be noted that the indication Lyme disease is not approved for penicillin V in all EU Member States (e.g. not approved in FR).

Furthermore, penicillin V is not included in the international general recommendations for the treatment of Lyme Disease (Wormser et al. 2006).

However, in analogy to amoxicillin which is recommended in Lyme Disease over a period of 14-21 days, we suggest a similar duration of 14-21 days.

Response from MAH 3 :

Duration of use

Penicillin V is generally given for 10 - 21 days for the treatment of erythema migrans (EM). However, the optimal duration of treatment has not been determined yet.

Only one study compared a two week and three week regimen of penicillin V for the treatment of EM (Aberer et al., 2006). The two-week treatment was as effective as the three-week course.

However, various published studies have shown good efficacy of penicillin V for the treatment of erythema migrans given either 10 days or 14 days. Treatment cure rates and the occurrence of minor or major manifestations of lyme borreliosis were similar both in patients treated 10 days or 14 days.

Based on the results of published studies, erythema migrans should therefore be treated with penicillin V for 10 - 14 days.

- Proposal for revision of the SmPC

Since the duration of treatment for EM is longer than the general recommendation (7-10 days) of the current SmPC, the MAH suggests in accordance with the assessor’s opinion to include a specific recommendation for the treatment of EM in section 4.2. of the SmPC e. g.

“Erythema migrans should be treated with penicillin V for 10 -14 days”.

Posology

The dosages used in the published studies are summarized in Table 5.

Table 5: Recommended dosages of penicillin V for the treatment of EM in adults and children, according to published studies

	Total daily dose	Frequency
Adults	Dosage varied from 3.0 mio to 4.5 mio IU* (1.8 g – 2.7 g)	divided in 3 doses
Children	100 000 IU (= 59 mg)/kg (max 3 mio IU) ⁺	divided in 3 doses

*in one published study a higher total daily dose of 2 g - 4 g (corresponding to 3.4 mio – 6.8 mio) was administered (Bennet et al., 2003).

⁺ in one published study a much higher dose (0.5 -0.8 mio IU/kg of body weight, 4 x day) was administered.

Proposal for revision of the SmPC

Adults

Based on the results of the published articles the effective dosage for treatment of EM in adults is 1.0 -1.5 mio units TID.

This dosage is already included in the “general broad recommendation” range for adults and children over 12 years of the current sanofi-aventis German SmPC of Isocillin:

“Depending on the severity and site of the infection, normally 295 – 885 mg (0.5 - 1.5 million units) phenoxymethylpenicillin are given 3 - 4 times daily.”

Children

The effective total daily dose for children for the treatment of EM according to the published literature is 100 000 IU/kg of body weight divided in three doses.

This dosage is higher than the general dosage recommendation of the current sanofi-aventis German SmPC of Isocillin which is about 60 000 IU/kg of body weight.

The MAH proposes to include the higher total daily dose of 100 000 IU/kg in the sanofi-aventis German SmPC of Isocillin for the treatment of EM in children:

“For the treatment of E.M. in children a daily dose of 100,000 IU/kg is recommended, divided in 3-4 single doses.”

Furthermore, due to the fact that E.M. will be explicitly mentioned in the dosage section the MAH also proposes to add E.M. as another special disease of the group of skin infections in the indications section.

Rapporteur’s final comments:

We agree with the MAHs, and specifically with one of the statements that any information on posology regarding this indication should only be added to the SmPC if the indication EM is covered by the marketing authorisation of the respective medicinal product.

However, regarding duration of treatment, according to the published articles regarding treatment of erythema migrans:

Treatment duration varies depending on the stage and severity of infection, and the age of the patient. Treatment of localized skin infections should continue for 14 days; treatment of early disseminated infection, for 21 days; treatment of acrodermatitis (which occurs predominantly in Europe), for 30 days; and treatment of Lyme disease-associated arthritis, for 30 to 60 days (Kasper et al., 2005). We agree with Sanofi-Aventis that the available documentation seems to support 10-14 days duration of therapy for EM. However, the necessary duration of

treatment of EM by penicillin V has not been adequately studied in clinical trials. Regarding dosage of penicillin for treatment of EM, one of the MAHs has provided the following publications: a) Arnez et al. 1999, b) Arnez et al. 2002, c) Arnez et al. 2001, d) Bennet et al. 2003, e) Strle et al. 1992, f) Krbkova and Stanek 1996, g) Maraspin 2002. Among these, the following studies; a, b, c and g were performed in children, and d, e and f were performed in adults which are not relevant in Article 45. The dosage in studies a, b, and c were 100.000 IU/kg/day in three equal doses. The dosage administered in study g is much higher (0.5-0.8 mio IU/kg of body weight) than the dosage used in papers a, b and c.

Most of the submitted studies seem to support 100.000 IU/kg/day in 3 equal doses, for 10-14 days. However, due to the different dose used in study g (Maraspin 2002), and the fact that one of the studies (Arnez *et al.* 2001) was designed to evaluate the benefit of identifying the causative agent, *Borrelia burgdorferi*, and not the effect of the treatment with penicillin V, there would seem to be a need for additional confirmatory studies.

V. RAPPORTEUR'S AND MEMBER STATES' OVERALL CONCLUSION AND RECOMMENDATION

Overall conclusion

The data from the submitted studies and scientific articles do not specifically suggest any need of major change in the current paediatric information in the SmPC for penicillin V. However, there are a few issues which should be specified in the SmPC.

We support the general comment from one of the MAH that the Article 45 work sharing is not intended to achieve full harmonization of the product information, and other applicable regulatory procedures should be considered.

Recommendation

The following SmPC and PL changes are proposed:

- To cover the possible differences in paediatric use of penicillin V in different member states due to the heterogeneous resistance situation in Europe, the following standard text is proposed to be added to the SmPC section 4.1 (if it is lacking): “*Consideration should be given to official guidance on the appropriate use of antibacterial agent*”.
- Based on the submitted documentation, the following information is proposed to be added in section 4.2 (if it is lacking): “*To avoid late complications (rheumatic fever), infections with β -haemolytic streptococci should be treated for 10 days*”.
- For medicinal products where acute otitis media is included in the indication, the following wording should be added in section 4.2: “*The treatment of acute otitis media with penicillin V should be limited to 5 days. However, 5-10 days treatment may be recommended in patients with potential for complications*”.

In addition to the above changes to SmPC and PL, authorisation holders are encouraged to conduct studies to provide information on the use of phenoxymethylpenicillin in the following circumstances:

Concomitant administration with food:

The compliance in children would be better if penicillin V is concomitantly administered with food. However, since both recommendations (intake with food /fasting intake of phenoxymethylpenicillin) are based on outdated data, new and more solid pharmacokinetic data on the interaction between food and drug is desirable.

Erythema migrans:

Treatment duration varies depending on the stage and severity of infection, and the age of the patient. Treatment of localized skin infections should continue for 14 days; treatment of early disseminated infection, for 21 days; treatment of acrodermatitis (which occurs predominantly in Europe), for 30 days; and treatment of Lyme disease-associated arthritis, for 30 to 60 days (Kasper et al. 2005). However, the necessary duration of antibiotic treatment has not been adequately studied in clinical trials. Therefore, there is need for clinical trials, which make basis for dose recommendation regarding EM.

Type IB variations on the proposed changes to the SmPC and PL should be submitted by the MAH concerned by 30.07.2010. For generic products: within 90 days of the published Public Assessment Report.

VI. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

According to submitted line listings: (All national MAs)

MAH	MS	Name of the medicinal product	Strength	Pharmaceutical form	Active Substance(s) Herbal MPs should be indicated (HERB)*	Marketing Authorisation Number
Aventis Pharma SA NV	BE	ORACILLINE	0.25 MIU	oral suspension	Phenoxymethylpenicillin	354 IS 383 F 8
Aventis Pharma SA NV	LU	ORACILLINE	0.25 MIU	oral suspension	Phenoxymethylpenicillin	0082961
Infectopharm Arzneimittel GmbH	DE	Infectocillin 1 Mega Filmtabletten	1 000 000 I.U./tablet	film-coated tablet	Phenoxymethylpenicillin potassium	6149647.00.00
Infectopharm Arzneimittel GmbH	DE	Infectocillin 1,5 Mega Filmtabletten	1 500 000 I.U./tablet	film-coated tablet	Phenoxymethylpenicillin potassium	42954.01.00
Infectopharm Arzneimittel GmbH	DE	Infectocillin 250 Saft	250 000 I.U./5 ml	powder for oral solution	Phenoxymethylpenicillin potassium	6149647.01.01
Infectopharm Arzneimittel GmbH	DE	Infectocillin 300 Saft	300 000 I.U./5 ml	powder for oral solution	Phenoxymethylpenicillin potassium	6061705.00.00
Infectopharm Arzneimittel GmbH	DE	Infectocillin 400 Saft	400 000 I.U./5 ml	granules for oral solution	Phenoxymethylpenicillin potassium	6156647.00.00
Infectopharm Arzneimittel GmbH	DE	Infectocillin 500 Saft	500 000 I.U./5 ml	powder for oral solution	Phenoxymethylpenicillin potassium	6149647.00.01

Infectopharm Arzneimittel GmbH	DE	Infectocillin Mio Tabs	1 000 000 I.U./tablet	soluble tablet	Phenoxymethylpenicillin potassium	6394192.00.00
Infectopharm Arzneimittel GmbH	DE	Penicillin V Infectopharm Tabletten	1 000 000 I.U./tablet	film-coated tablet	Phenoxymethylpenicillin potassium	43671.00.00
Recip AB, Sweden	SE	Kåvepenin Recip	125 mg	film-coated tablet	phenoxymethylpenicillin potassium	10334
Recip AB, Sweden	DK	Primcillin	250 mg	filmcoated tablets	phenoxymethylpenicillin kalium	11875
Sandoz GmbH		OSPEN 750	750 000 IU/5 ml	oral suspension	Phenoxymethylpenicillinum kalicum	R/3632
Sandoz GmbH	LT	OSPEN 750	750 000 IU/5 ml	oral suspension	Phenoxymethylpenicillinum kalicum	R/3632
Sandoz GmbH	PL	OSPEN 750	750 000 IU/5 ml	oral suspension	Phenoxymethylpenicillinum kalicum	R/3632
Sandoz GmbH	EL	OSPEN	400.000 IU/5ML	ORAL SUSP.	Phenoxymethylpenicillin benzathine	24522/2000/14-2-2001 & 55057/7-10-2004 Change of MAH
Sandoz GmbH	BG	Ospen	0,4 MIU / 5 ml	Oral suspension	Phenoxymethylpenicillin benzathine	20000306
Sandoz GmbH	BG	Ospen	0,75 MIU / 5 ml	Oral suspension	Phenoxymethylpenicillin benzathine	20000305
Sandoz GmbH	PL	OSPEN 750	750 000 IU/5 ml	oral suspension	Phenoxymethylpenicillinum kalicum	R/3632
Sandoz GmbH		OSPEN 750	750 000 IU/5 ml	oral suspension	Phenoxymethylpenicillinum kalicum	R/3632
Sanofi-Aventis Deutschland GmbH	DE	ISOCILLIN 1,2 MEGA	1200000 IU	film-coated tablet	Phenoxymethylpenicillin	6132032.01.00
Sanofi-Aventis Deutschland GmbH	DE	ISOCILLIN SAFT	150000 IU	powder for oral solution	Phenoxymethylpenicillin	14014.00.00

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