Public Assessment Report

Scientific discussion

Pikopil 5 mg and 7.5 mg tablets
Pikopil oral drops 7.5 mg/ml, solution

(sodium picosulphate)

NL/H/3235/001-003/DC

Date: 1 August 2016

This module reflects the scientific discussion for the approval of Pikopil 5 mg and 7.5 mg tablets and Pikopil oral drops 7.5 mg/ml, solution. The procedure was finalised on 22 December 2015. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.
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<th>Abbreviation</th>
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<td>ASMF</td>
<td>Active Substance Master File</td>
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<td>BP</td>
<td>British Pharmacopoeia</td>
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<td>CHMP</td>
<td>Committee for Medicinal Products for Human Use</td>
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<td>CMD(h)</td>
<td>Coordination group for Mutual recognition and Decentralised procedure for human medicinal products</td>
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<td>CMS</td>
<td>Concerned Member State</td>
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<td>EDMF</td>
<td>European Drug Master File</td>
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<td>EDQM</td>
<td>European Directorate for the Quality of Medicines</td>
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<td>EEA</td>
<td>European Economic Area</td>
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<td>ERA</td>
<td>Environmental Risk Assessment</td>
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<td>ICH</td>
<td>International Conference of Harmonisation</td>
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<td>MAH</td>
<td>Marketing Authorisation Holder</td>
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<td>Ph.Eur.</td>
<td>European Pharmacopoeia</td>
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<td>PL</td>
<td>Package Leaflet</td>
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<td>RH</td>
<td>Relative Humidity</td>
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<td>RMP</td>
<td>Risk Management Plan</td>
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<td>SmPC</td>
<td>Summary of Product Characteristics</td>
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<td>TSE</td>
<td>Transmissible Spongiform Encephalopathy</td>
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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Pikopil 5 mg and 7.5 mg tablets, and Pikopil oral drops 7.5 mg/ml, solution from Vital Pharma GmbH.

The product is indicated for the short term relief of chronic or habitual constipation.

The tablet form is indicated in adults and in children aged from 4 years.

The solution form is indicated in all ages.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a hybrid application claiming essential similarity with the innovator product Dulco drops 7.5 mg/ml (NL License RVG 6319) which has been registered in Netherlands by Boehringer Ingelheim B.V. since 1 December 1971. Boehringer Ingelheim also registered several tablet forms of Dulco drops in member states, including Dulcolax and Laxoberal.

The concerned member state (CMS) involved in this procedure is Poland.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, a hybrid application, as for locally acting medicinal products bioequivalence cannot be demonstrated through bioavailability studies.

II. QUALITY ASPECTS

II.1 Introduction

Pikopil 5 mg and 7.5 mg tablets

White to off-white, round, flat bevelled-edge tablets with a score line. The tablet can be divided into equal doses. Each tablet contains sodium picosulphate monohydrate equivalent to 5 mg or 7.5 mg sodium picosulphate (anhydrous). The two tablet strengths are dose proportional.

The tablets are packed in a colourless PVC/Aluminium foil blister.

The excipients are: lactose monohydrate, maize starch, pregelatinised maize starch, colloidal anhydrous silica, magnesium stearate (E572).

Pikopil oral drops 7.5 mg/ml, solution

Clear colourless or yellowish solution. 1 ml contains sodium picosulphate monohydrate equivalent to 7.5 mg sodium picosulphate anhydrous (1 ml equals 15 drops).

The solution is packed in a white opaque polyethylene dropper container with green tamper-evident cap containing 15 ml or 30 ml oral solution.

The excipients are: sodium benzoate (E211), sorbitol (E420), citric acid monohydrate (E330), sodium citrate (E331), water for injections.

II.2 Drug Substance

The active substance is picosulphate monohydrate, an established active substance described in the European and British Pharmacopoeia (Ph.Eur., BP). The active substance is freely soluble in water. The substance show polymorphism and the form produced is consistent. The molecule contains no chiral centres.
The Active Substance Master File (ASMF) procedure is used for both active substances. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or ‘know-how’ of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

**Manufacturing process**
The manufacturing process consists of three steps (manufacturer-I) or two steps (manufacturer-II). The proposed starting materials are considered simple structural structures and acceptable. No metal catalysts or class 1 solvents are used. The active substance has been adequately characterised and acceptable specifications have been adopted for the starting material, solvents and reagents.

**Quality control of drug substance**
The drug substance specification is in line with the Ph.Eur. monograph with additional requirements for residual solvents. The additional requirements for residual solvents are in line with the specifications of the ASMF holders. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full scale batches of each supplier.

**Stability of drug substance**

*Manufacturer-I*
Stability data on the active substance have been provided for 12 full scale batches stored at 25°C/60% RH (12-60 months) and three full scale batches at 40°C/75% RH (6 months). All parameters tested remain relatively stable at both storage conditions. Based on the stability data provided the proposed re-test period of 36 months without special storage conditions can be granted.

*Manufacturer-II*
Stability data on the active substance have been provided for three full scale batches stored at 25°C/60% RH (48 months) and at 40°C/75% RH (6 months). All parameters tested remain relatively stable at both storage conditions. Based on the stability data provided the proposed re-test period of 60 months stored protected from light can be granted.

**II.3 Medicinal Product**

*Pikopil 5 mg and 7.5 mg tablets*

**Pharmaceutical development**
The products are established pharmaceutical forms and their development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The MAH has adequately demonstrated that the disintegration time, friability and subdivision are acceptable. The main development studies were formulation trials and comparative dissolution studies with the German innovator product, Laxoberal. The pharmaceutical development of the product has been adequately performed.

Bioequivalence studies are not performed as the drug substance acts locally in the intestine and the colon. Of each tablet strength the dissolution profiles of 3 batches were tested in three buffer media. Dissolution profiles for Pikopil 5 mg and 7.5 mg tablets show that the products are rapidly and completely dissolving at pH 1.2, 4.5, and 6.8.

**Manufacturing process**
The manufacturing process consists of mixing, wet granulation, lubrication and compression. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three (5 mg) and four (7.5 mg) full scale batches in accordance with the relevant European guidelines. The product is manufactured using conventional manufacturing techniques.
Control of excipients
The excipients comply with the requirements of their respective Ph.Eur. monographs. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identification, weight, related substances, disintegration, uniformity of dosage units, microbial quality and assay. The release and shelf life limits are identical except for related substances. The drug product specification is acceptable.
The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on four full scale batches of each strength, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product has been provided four full scale batches of each strength stored at 25°C/60% RH (18 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in PVC/Al blister.
Increases in impurities were observed. All other parameters tested remained relatively stable throughout the test periods at both test conditions and within specification limits. Photostability studies, in line with ICH conditions, were performed on two 5 mg batches. No degradation was observed. Based on the stability data provided, a shelf life of 18 months without special storage conditions can be granted.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopaties
None of the excipients used is of animal or human origin except for lactose. The milk is sourced from healthy animals in the same conditions as milk collected for human consumption (EMEA/410/01 rev 2) and the lactose is prepared without the use of other ruminant materials than calf rennet. The calf rennet is in accordance with Public Statement EMEA/CPMP/571/02.

Pikopil oral drops 7.5 mg/ml, solution

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies performed were comparative analysis of physicochemical properties as bioequivalence studies cannot be performed with the drug product at issue. The drug product and the reference product were compared with respect to qualitative composition, quantitatively regarding sodium benzoate and sorbitol, appearance, clarity, coloration, density, pH, related substances, viscosity, osmolality and uniformity of dosage units. Dose and uniformity of dose of oral drops in accordance to the Ph.Eur. has been demonstrated of the dropper.
The delivered volume of 1 ml is equivalent to 15 drops as for the reference product.
The drug product contains 7.5 mg/ml sodium picosulphate (as monohydrate), whereas the reference product contains 7.5 mg/ml sodium picosulphate monohydrate equivalent to 7.23 mg/ml sodium picosulphate. Pikopil oral drops is a hybrid application, therefore the content active substance of the product does not have to be identical to that of the innovator. Given the acceptable range for assay 95 – 105%, the content of the drug product is within this range.
The pharmaceutical development of the product has been adequately performed. The drug product is considered therapeutic equivalent to the reference product.

Manufacturing process
The manufacturing process consists of dissolving components in water, pre-filtration, filtration and filling. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for two pilot scale batches of each fill volume. The product is manufactured using conventional manufacturing techniques. Process validation for full scaled batches will be performed post authorisation.
Control of excipients
The excipients comply with the requirements of their respective Ph.Eur. monographs. These specifications are acceptable.

Microbiological attributes
Data has been provided demonstrating that the addition of a preservative is necessary. The efficacy of the antimicrobial preservation has been tested in line with the Ph.Eur. for 90% and 100% of the nominal sodium benzoate concentration. Microbial testing is included in the drug product specification and the formal stability studies. The test is performed as per Ph.Eur.

Quality control of drug product
The product specification includes tests for appearance, identification of sodium picosulphate and sodium benzoate, clarity, coloration, density, pH, dose and uniformity of dose of oral drops, extractable volume, related substances, microbial quality, assay of sodium picosulphate and sodium benzoate. The release and shelf life limits are identical except for coloration and related substances. The specification is acceptable. The analytical methods have been adequately described and validated.
Batch analytical data from the proposed production site have been provided on two pilot scale batches of each fill volume, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided two pilot batches of each fill volume stored at 25°C/60% RH (18 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. One batch of the 30 ml fill volume was stored inverted.
Increases in impurities were observed. All other parameters tested remained relatively stable throughout the test periods at both test conditions and within specification limits.
Photostability studies, in line with ICH Q1B, were performed on two batches of the 30 ml fill volume. No degradation was observed.
Based on the stability data provided the proposed shelf life of 30 months without special storage conditions can be granted.
Furthermore, in-use stability studies were performed on to batches of 30 ml. The batches were opened once every month, stored inverted at long term conditions and tested after 3, 6, 9 and 12 months of storage. The trends observed were similar to the unopened batches. Based on the in-use stability data provided an in-use shelf life of 12 months without special storage conditions can be granted.
Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects
Based on the submitted dossier, the member states consider that Pikopil has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.
No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)
Since Pikopil is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.
III.2 Discussion on the non-clinical aspects

This product is a hybrid formulation of Dulco drops which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Sodium picosulphate is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

Biowaiver

Pikopil is registered as a hybrid medicinal product as it acts locally in the colon. Hence sodium picosulphate is almost not absorbed. The drug substance is metabolised in the colon and the metabolite acts locally. The MAH has not submitted bioequivalence studies, but requested for biowaivers for the tablets and oral drops.

Pikopil 5 mg and 7.5 mg tablets

A BCS-Class III based biowaiver is requested, for which comparison is made to Laxoberal tablets (Boehringer Ingelheim Pharma, Germany) as the reference drug product. The 5 mg drug product was selected for comparative studies, as Laxoberal, 7.5 mg tablets is not available on the market. The 5 mg and 7.5 mg tablets have the same dose-proportional composition.

The following criteria were fulfilled:

- Dissolution profiles for Pikopil 5 mg and 7.5 mg tablets confirm that the products are rapidly and completely dissolving at pH 1.2, 4.5, and 6.8. Very rapid (>85 % within 15 min) \textit{in vitro} dissolution of the test and reference product has been demonstrated considering specific requirements
- Excipients that might affect bioavailability are qualitatively and quantitatively the same and other excipients are qualitatively the same and quantitatively very similar.

Based upon solubility data (BCS Class III drug), the very rapid dissolution, the fact that sodium picosulphate is almost not absorbed, and excipients which are considered not to affect absorption (if any) and transit, the Pikopil tablets are considered to have similar pharmacokinetics (if any), safety and efficacy compared to the reference products.

Pikopil oral drops 7.5 mg/ml, solution

This application concerns a 7.5 mg/ml oral solution for which the MAH requested a biowaiver with the Dulco drops 7.5 mg/ml as reference. Essential similarity with the originator product is based on comparative qualitative attributes of the product. The Guideline on requirements for locally applied, locally acting products, containing known constituents (CPMP/239/95) states that in order to demonstrate therapeutic equivalence clinical trials are in principal necessary, but other models may be used or developed. Overall, the test formulation is comparable to the reference formulation considering their qualitative and quantitative composition. The biowaiver for Pikopil oral drops 7.5 mg/ml is acceptable.
IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Pikopil.

Summary table of safety concerns as approved in RMP:

| Important identified risks                                                                 | • Bowel obstruction and intestinal perforation in patients with pre-existing intestinal obstruction of any kind of origin (ileus, intestinal obstruction, acute abdominal conditions including appendicitis, acute inflammatory bowel diseases) |
|                                                                                        | • Severe dehydration                                      |
|                                                                                        | • Hereditary conditions incompatible with an excipients    |
|                                                                                        | • Hypersensitivity to any ingredient of the products       |
|                                                                                        | • Overdose, prolonged excessive use                        |
| Important potential risks                                                             | • Fluid and electrolyte imbalance, severe impaired renal function |
|                                                                                        | • Dizziness and/or syncope                                |
|                                                                                        | • Concomitant intake of drugs where hypokalaemia is a particular risk, e.g. cardiac glycosides |
| Missing information                                                                   | • Pregnancy                                              |

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Dulco drops. No new clinical studies were conducted. The MAH provided sufficient comparative quality data in support of a biowaiver. Risk management is adequately addressed. This hybrid medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) of Pikopil oral drops 7.5 mg/ml, solution has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of: a pilot test with 2 participants, followed by two rounds with 10 participants each. The submitted report is considered acceptable. Overall the test participants were satisfied with the readability of the text. They were also satisfied with the clarity of the text, the graphical layout and the font style/size. The PL of Pikopil oral drops 7.5 mg/ml, solution meets the criteria as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

A user consultation with target patient groups on the PL of Pikopil tablets has been performed on the basis of a bridging report making reference to the PL of Pikopil oral drops. Hence Pikopil oral drops 7.5 mg/ml, solution and Pikopil tablets contain sodium picosulphate as active substance, have the same indication, and the same target patient population. The information concerning safe and effective use of both medicinal products is therefore merely the same. Both PLs are written in plain language and in the same style of writing. Design and layout of both “parent” and “daughter” PLs is identical. The bridging report submitted by the MAH has been found acceptable.
VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Pikopil 5 mg and 7.5 mg tablets and Pikopil oral drops 7.5 mg/ml, solution have a proven chemical-pharmaceutical quality and are hybrid forms of Dulco drops. Dulco drops is a well-known medicinal product with an established favourable efficacy and safety profile.

Since Pikopil is intended to act locally in the colon without systemic absorption and has a comparable composition to the reference products, no bioequivalence study is deemed necessary.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Pikopil with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 22 December 2015.
### STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE – SUMMARY

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