SCIENTIFIC DISCUSSION

This part reflects the scientific knowledge and the information about this product available at the time of prequalification. Thereafter, updates may have become necessary which are included in parts 1 to 5 and, if related to pharmaceutical issues, also documented in part 8 of this WHOPAR.

Name of the Finished Pharmaceutical Product:	Para-aminosalicylate sodium delayed-release granules 60% w/w
Manufacturer of Prequalified Product:	Macleods Pharmaceuticals Ltd Phase II, Plot 25-27 Sr No. 366, Premier Ind. Estate, Kachigan, Daman (U.T.) 396 21 India
Active Pharmaceutical Ingredient (API):	Para-aminosalicylate sodium
Pharmaco-therapeutic group (ATC Code):	Drugs for treatment of tuberculosis, Aminosalicylic acid and derivatives (J04AA02)
Therapeutic indication:	Para-aminosalicylate sodium 60% delayed-release granules is indicated in combination with other antituberculosis agents for the treatment of all forms of tuberculosis caused by *Mycobacterium tuberculosis.* Para-aminosalicylate sodium 60% delayed-release granules is only indicated as a second-line antimycobacterial drug when use of first line drugs is not appropriate due to resistance or intolerance.

1. Introduction

Para-aminosalicylate sodium delayed-release granules 60% w/w is indicated in combination with other antituberculosis agents for the treatment of all forms of tuberculosis caused by *Mycobacterium tuberculosis.*Para-aminosalicylate sodium delayed-release granules 60% w/w is only indicated as a second-line antimycobacterial drug when use of first line drugs is not appropriate due to resistance or intolerance.
Para-aminosalicylate sodium delayed-release granules 60% w/w is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients, and in patients with severe renal impairment
It is recommended that therapy is given only on the advice of a physician experienced in the treatment of tuberculosis.

2 Assessment of Quality

The assessment was done according to SOP 20 of the WHO Prequalification programme.

Active pharmaceutical Ingredient (API)

Para-aminosalicylate sodium (PAS sodium) is described in the Ph.Eur. (as Sodium Aminosalicylate Dihydrate) and in the USP (as Aminosalicylate Sodium). It is freely soluble in water, and sparingly soluble in alcohol.
The API is manufactured in multiple steps from meta-aminophenol and purified by means of recrystallisation. Control of the starting material, intermediates, solvents and reagents is regarded adequate. The API is controlled by pharmacopoeial based specifications, with an additional in-house specification for residual solvents.
Based on the results of stability testing conducted according to the requirements of WHO, a retest period of 6 months was approved for PAS sodium when stored below 25^{o}C in a dry place protected from light.

Other ingredients

Other ingredients used in the core granule formulation include butylated hydroxytoluene, crospovidone, hydrogenated castor oil, hydrogenated vegetable oil, microcrystalline cellulose and sodium metabisulphite. Ingredients used in the coating and polishing steps include colour iron oxide red, colour quinoline yellow supra, dibutyl phthalate, ethylcellulose, hydrogenated vegetable oil, methacrylic acid-methyl methacrylate copolymer, purified talc, stearic acid and titanium dioxide.

Finished pharmaceutical product (FPP)

Pharmaceutical development
Para-aminosalicylate sodium 60% granules is not describe in any of the recognized pharmacopoeia. Aminosalicylate Sodium Tablets appears in the USP.
Para-aminosalicylate sodium 60% granules are brick-red coloured enteric coated granules. The granules (100g) are packaged in a LDPE bag, placed in a triple laminated Alu/PET/Alu/LLDPE sachet which is further placed in a white opaque HDPE bottle fitted with a PP closure (pack size: 100gm).
The development of the final composition of Para-aminosalicylate sodium 60% granules has been described and the compatibility of the API with the excipients demonstrated. To protect the API from oxidation, sodium metabisulphite and butylated hydroxytoluene are included in the core granules, which are prepared through a process of wet extrusion, followed by spheronization. Studies were conducted at pilot scale level to optimise the extrusion and spheronization parameters. The core granules are coated with seal and enteric coatings and finally polished.
Appropriate in-process controls have been set to ensure batch-to-batch reproducibility. Validation data presented on three production batches and batch analysis data demonstrate the consistency of the

process and the quality of the product. The specifications are considered adequate for controlling the quality of this finished pharmaceutical product at release and during shelf life.

Stability testing
Stability studies have been performed on the same three batches used for process validation at 25°C/60%RH as long-term conditions and at accelerated conditions according to the requirements of WHO. At the time of the prequalification, a shelf-life of 24 months has been allowed for the FPP when stored at a temperature not above 25°C, with a 10 day use period after first opening of the sachet.

Conclusions

The quality part of the dossier is accepted.

3. Assessment of Bio-Equivalence

Two bioavailability studies, one under fasting and one under fed conditions have been performed in 2005 and 2008 respectively, according to internationally accepted guidelines. The aim of the fasting study was to obtain at the end of the dose interval a concentration of at least 1 µg/ml (MIC for M. Tuberculosis). The aim of the fed study was to evaluate the food effect on the delayed-release granules.

Fasting study:
Comparative pharmacokinetic study of para amino salicate sodium granules 60% w/w (delayed-release) manufactured by Macleods Pharmaceuticals LTD, India with Paser, amino salicylic acid delayed-release granules manufactured by Jacobus Pharma U.S.A. in 24 + 2 standbyes healthy, adult, male subjects in a randomised crossover study in fasting conditions (study no. PDWH002).

The objective of the study was to compare the bioavailability of the stated delayed-release para-amino salicate sodium granules 60% w/w (4.78 grams para amino salicylic acid) manufactured by Macleods Pharmaceuticals LTD, India (test drug) with the reference formulation Paser (4 grams amino salicylic acid delayed-release granules manufactured by Jacobus Pharma) and to assess bioavailability. The comparison was performed as a single centre, open label, randomised, single dose, crossover study in healthy male subjects under fasting conditions. Each subject was assigned to receive one of the following two treatments:

Treatment T:	Test – Delayed-release para amino salicate sodium granules 60% w/w (4.78 grams amino salicylic acid dealyed realse granules) Batch no. PF410.
Treatment R:	Reference – Paser® delayed-release granules (4 grams amino salicylic acid delayed-release granules) Batch no. 10612.

A 7 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 12 samples within 13 h post dose) were taken during each study period to obtain bioavailability characteristics AUC and C_{max} in addition to t=13h values for bioavailability evaluation. Drug concentrations for amino salicylic acid were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 498 ng/ml for amino salicylic acid.

The study was performed with 26 participants; data generated from a total of 24 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for amino salicylic acid as well as statistical results are summarised in the following tables:

Amino salicylic acid

Pharmacokinetic Parameter	Test formulation (T) arithmetic mean ± SD (*)	Reference (R) arithmetic mean ± SD (*)	log-transformed parameters#	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
C_{max} (µg/ml)	21.4 ± 10.9 (15.8)	17.6 ± 8.9 (15.6)	101.3	84.0 – 122.0
AUC_{0-t} (µg.h/ml)	108.7 ± 49.7 (82.7)	86.8 ± 34.5 (80.7)	102.4	89.9 – 116.6
AUC_{0-inf} (µg.h/ml)	120.9 ± 53.8 (92.2)	111.5 ± 50.5 (101.9)	90.5	77.2 – 106.0

* dose normalised geometric mean; # dose normalied

The mean plasma concentrations at the end of the dosing interval (13 h after administration) of the test and reference was 4.365 ± 2.892 µg/ml and 3.392 ± 2.251 µg/ml, respectively, which is above the MIC of 1 µg/ml for M. Tuberculosis.

Fed study:
The objective of the study was to compare the bioavailability of the stated delayed-release para amino salicate sodium granules 60% w/w (4.78 grams para amino salicylic acid) manufactured by Macleods Pharmaceuticals LTD, India (test drug) under fed and fasting conditions. The comparison was performed as a single centre, open label, randomised, single dose, crossover study in healthy male subjects (study no. BEQ-136-PARA-2007).

Twenty-eight (24 + 4 standbyes) healthy volunteers were included in this study and received the drug under fasting conditions (overnight fast) or under fed conditions (high fat, high caloric breakfast) with 240 ml orange juice. A 7 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 21 samples within 24 h post dose) were taken during each study period to obtain bioavailability characteristics AUC and C_{max}. Drug concentrations for amino salicylic acid were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 196 ng/ml for amino salicylic acid.

The study was performed with 28 participants; data generated from a total of 24 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioavailability.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for amino salicylic acid as well as statistical results are summarised in the following tables:

Amino salicylic acid

Pharmacokinetic Parameter	Test formulation fasting arithmetic mean ± SD	Reference fed arithmetic mean ± SD	log-transformed parameters#	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
C_{max} (µg/ml)	22.6 ± 9.3	38.8 ± 16.4	174	147 – 202
AUC_{0-t} (µg.h/ml)	112.6 ± 52.2	168.5 ± 67.9	155	136 – 174
AUC_{0-inf} (µg.h/ml)	113.8 ± 51.9	169.5 ± 67.9	154	135 – 173

Conclusions:

The results of the fasting study show that bioequivalence could be proven for the dose normalised AUCt and Cmax values regarding amino salicylic acid. Furthermore, mean plasma concentrations at the end of the dosing interval (13 h after administration) of the test and reference were above the MIC of 1 µg/ml for M. Tuberculosis.

The chosen test formulation and dose, and the outcome of the fasting study support the dose recommendations according to the "WHO Guideline for the programmatic management of drug resistant tuberculosis (Emergency Update, 2008)" and the WHO document "Management of MDR-TB: A Field Guide (2010)".

The results of the fed study show that a high fat meal increases AUC and Cmax of amino salicylic acid by 55 and 74%, respectively.

4. Summary of Product Safety and Efficacy

Para-aminosalicylate sodium 60% granules has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the innovator product. According to the submitted data on quality and bioavailability Para-aminosalicylate sodium 60% granules is pharmaceutically and therapeutically equivalent and thus interchangeable with the innovator product Paser® for which benefits have been proven in terms of clinical efficacy.

The clinical safety of this product is considered to be acceptable when guidance and restrictions stated in the Summary of Product Characteristics are considered. Reference is made to the SPC (WHOPAR part 4) for data on clinical safety.

5. Benefit risk assessment and overall conclusion

Quality

Physicochemical and biological aspects relevant to the uniform pharmaceutical characteristics have been investigated and are controlled in a satisfactory way. The quality of this product is considered to lead to an acceptable clinical performance when Para-aminosalicylate sodium 60% granules is used in accordance with the conditions as stated in the SPC.

Bioequivalence

Para-aminosalicylate sodium 60% granules has shown to be bioequivalent with Paser® delayed-release granules (Jacobus Pharma, U.S.A.).

Efficacy and Safety

Regarding clinical efficacy and safety, Para-aminosalicylate sodium 60% granules is considered effective and safe to use when the guidance and restrictions presented in the Summary of Product Characteristics are considered.

Benefit Risk Assessment

Based on the WHO's assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit risk profile of Para-aminosalicylate sodium 60% granules was acceptable for the following indication: **"in combination with other antituberculosis agents for the treatment of all forms of tuberculosis caused by *Mycobacterium tuberculosis*, as a second-line antimycobacterial drug when use of first line drugs is not appropriate due to resistance or intolerance"** and has advised that the quality, efficacy and safety of Para-aminosalicylate sodium 60% granules are acceptable to allow inclusion of Para-aminosalicylate sodium 60% granules, manufactured at Macleods Pharmaceuticals Ltd, Phase II Plot 25-27 Sr No. 366, Premier Ind. Estate Kachigan, Daman (U.T.), 396 21 India in the list of prequalified medicinal products.