STATE INSTITUTE FOR DRUG CONTROL
Kvetná 11, 825 08 Bratislava 26, Slovak Republic

Public Assessment Report

Scientific discussion

Kyselina acetylsalicylová Xantis 100 mg
Acetylsalicylic acid

SK/H/0187/001/DC

Date: 05.02.2018

This module reflects the scientific discussion for the approval of Kyselina acetylsalicylová Xantis 100 mg. The procedure was finalised at 05.01.2018. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Kyselina acetylsalicylová Xantis 100 mg, tablets from XANTIS PHARMA LIMITED, Nicosia, Cyprus.
The product is indicated for *unstable angina pectoris, acute heart attack, prevention of re-infarction, after surgery or other intervention on arteries, prevention of transient ischemic attacks (TIA) and strokes after previous signs.*
A comprehensive description of the indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(a) of Directive 2001/83/EC. Over the years of world-wide use it has been proven that acetylsalicylic acid is well tolerated by the patients. Acetylsalicylic acid possesses a profile of a safe drug substance, fulfilling the criteria of the well-established medicinal use. The pre-clinical tests or clinical trials can be replaced by appropriate scientific literature when applicant demonstrates that the medicinal product is in well-established medicinal use within the Community for at least ten years.

II. QUALITY ASPECTS

II.1 Introduction

Kyselina acetylsalicylová Xantis 100 mg is a solid oral dosage form (tablet). The product is formulated as white to off-white, round, lenticular tablet, half-scored on one side, diameter 7 mm. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses. Tablets are manufactured by direct compression. Tablets are packed in transparent blisters consisting of PVC foil coated with PVdC and aluminium foil with thermoforming layer. Carton box has been chosen as a secondary packaging. Shelf-life of 36 months with "*Store below 30 ºC. Store in the outer package in order to protect from moisture"* is approved.

II.2 2.2 Drug Substance

Acetylsalicylic acid; 2-(Acetyloxy)benzoic acid

- ***Appearance*:** white or almost white, crystalline powder or colourless crystals
- ***Solubility*:** slightly soluble in water, freely soluble in ethanol (96 per cent)
  non-chiral molecule
- ***Manufacturing:*** The drug substance is described in the European Pharmacopoeia. The manufacturer NOVACYL France is holder of valid certificate of suitability from EDQM. The re-test period of the substance as stated on the CEP is 36 months if stored at a temperature not exceeding 25°C in low-density polyethylene bags kept in fibre drums or in polypropylene big bags. It is mentioned that the holder of the CEP has declared the absence of use of material of human or animal origin in the manufacture of the substance.
- ***Specification:*** The ASA is controlled according to the current European Pharmacopoeia monograph for acetylsalicylic acid (Ph. Eur. No: 0309).
- ***Stability:*** Stability information's has been assessed during the certification process.

II.3 Medicinal Product

Pharmaceutical development and manufacturing process:
The objective was to develop formulation of solid dosage form with good stability and suitable physical properties. All the excipients (maize starch and powdered cellulose) used in the tablets are common in solid oral dosage forms and are of pharmacopoeial quality. Novel excipients are not used.

Tablets are manufactured by direct compression. First steps of manufacturing process are weighing and sieving of starting raw materials followed by mixing in a slow speed homogeniser with final compression into round, lenticular, half-scored tablets.
As per the dissolution profiles, Kyselina acetylsalicylová Xantis 100 mg disintegrates rapidly. The formulation of the tablets allows a rapid release of the API. With regards to high solubility and permeability of API (assigned to Class I of the Biopharmaceutics Classification System (BCS)), Kyselina acetylsalicylová Xantis 100 mg is likely to exert the pharmacokinetic profile comparable with the API formulations described in the scientific literature. The dissolution profiles of Kyselina acetylsalicylová Xantis 100 mg in different dissolution media (0.1 M hydrochloric acid; acetate buffer pH 4.5; phosphate buffer pH 6.8) according to dissolution method, stated in the specification performed from 6 units were presented. Kyselina acetylsalicylová Xantis 100 mg dissolved within 30 minutes at 50 rpm more than 85 % of the labelled amount of API in all tested media.

Stability:
Three batches have been stored under LT, AC and intermediate conditions. Following parameters were investigated during stability studies: appearance, average mass of 1 tablet, dissolution, related substances, assay of ASA, loss on drying, resistance to crushing, microbiological purity.

Kyselina acetylsalicylová Xantis 100 mg underwent photostability testing. Drug product remained chemically and physically stable outside of the immediate pack, in blister and directly exposed under the photo stability condition.

Stress testing has been performed in the validation of HPLC method for related substances. Degradation has been observed at high temperature and under wet, acidic, alkaline and oxidative conditions.

According to submitted data a shelf life of 36 months with "*Store below 30 ºC. Store in the outer package in order to protect from moisture"* is approved.

III. NON-CLINICAL ASPECTS

III.1 Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided as a literature review, which refers to 115 publications up to year 2015.

III.2 Pharmacology

Acetylsalicylic acid (ASA) belongs to the group of non-steroidal anti-inflammatory drugs (NSAIDs) and has analgesic, anti-inflammatory and antipyretic properties; it acts as an inhibitor of the enzyme cyclo-oxygenase (COX), which results in the direct inhibition of the biosynthesis of prostaglandins and thromboxanes from arachidonic acid. ASA also inhibits platelet aggregation due to the ability to acetylate proteins and is thus used in cardiovascular indications.

Acetylsalicylic acid shows effects on hemostasis by impairing platelet aggregation via inhibition of platelet thromboxane A_2 synthesis, thus reducing thrombus formation on the surface of the damaged arterial wall. Growing evidence also indicates that ASA exerts additional antithrombotic effects, which appear to some extent unrelated to platelet thromboxane A_2 production. ASA can reduce thrombin generation with the subsequent attenuation of thrombin-mediated coagulant reactions such as factor XIII activation. ASA also acetylates lysine residues in fibrinogen resulting in increased fibrin clot permeability and enhanced clot lysis. ASA treatment therefore resulted in a decreased stability of the clots as evidenced by their higher solubility.

III.3 Pharmacokinetics

Absorption: Following oral administration, blood ASA concentration rose sharply, reaching a maximum in about 5 to 7 min and then declined rapidly, with only trace amounts remaining after 30 min.
Distribution: Once absorbed, ASA is rapidly hydrolysed to salicylic acid with a half-life of only 15 to 20 min. Thus, from this stage onwards the pharmacokinetics of ASA, and other salicylates hydrolysed to salicylic acid, are predominantly dependent upon the salicylate moiety.
Salicylic acid is normally highly protein bound (80 to 90%) at therapeutic plasma concentrations and this probably accounts for the low reported values for the apparent volume of distribution.
Metabolism: ASA is hydrolyzed to salicylic acid (SA), which is further metabolized by conjugation to form salicyluric acid (SU), salicyl phenolic glucuronide and salicyl acyl glucuronide. To a minor extent, SA is hydroxylated to form gentisic acid, some of which is conjugated with glucuronide to form gentisuric acid.
Excretion: After a single oral dose (10, 20, 50 or 100 mg/kg) of ^{14}C-ASA to rats, most of the administered radioactivity was rapidly eliminated in the urine. Collected over 3 days, the mean recovery in the groups was 95.6-98.8% with 80.1-90.8%, in the first 24 h.

III.4 Toxicology

Teratogenic effects of salicylates have been observed in animal studies and on a number of different species. After prenatal exposure have been reported implantation defects, embryotoxic and foetotoxic effects and in offspring was impaired learning ability. Acetylsalicylic acid is sufficiently tested to mutagenesis in vitro and in vivo. There was no significant evidence of a mutagenic potential originating from pre-clinical data. The same also applies to carcinogenicity studies.
Genotoxicity
In vitro DNA-repair tests have not shown any signs of genotoxicity.
Carcinogenicity
The results of chronic toxicity studies indicate that ASA had not any influence on the incidence of mammary carcinoma in any of the concentrations studied.
Reproductive and developmental toxicity
Salicylates are among the oldest and most widely used drugs and are known to lead to foetal death, growth retardation and congenital abnormalities in experimental animals. Although teratogenic effects were observed in rats and dogs studies, an oral dose of 30 mg sodium salicylate/kg could be accepted as a no-observed-effect level (NOEL) for teratogenicity.
Fertility and early embryonic development
Embryotoxicity and foetotoxicity studies in dogs, mice and rats resulted in a high incidence of stillborns in dogs and of resorption in mice and rats. In the rabbit reduced fertility and abnormal blastocysts have been shown.
Embryo-foetal development
A significant dose-related reduction in foetal weight and significant increases in delayed ossification of the limbs and vertebrae were observed in oral teratology studies. The following effects on embryo-foetal development were observed: anophthalmia, acute reduction of heart beat, oedematous facial malformations and abnormality of tail (in rats); cleft palate, micrognathia, anasarca, cardiovascular malformations and tail malformations (in dogs).

Prenatal and postnatal development, including maternal function
ASA decreased the total brain weight, cerebrum length and width, and decreased the cerebellum length and width at ASA dose of 37.5 mg/kg.

III.5 Ecotoxicity/environmental risk assessment (ERA)

Applicant has provided reasoning why an ERA is not necessary for marketing authorisation of medicinal product Kyselina acetylsalicylová Xantis 100 mg. This rational is mainly based on the assumption that Kyselina acetylsalicylová Xantis 100 mg will be used as an alternative medicinal product to existing medicinal products and thus no increase in environmental risk is expected.

IV. CLINICAL ASPECTS

IV.1 Introduction

The clinical overview refers to 200 references dated up to 2017. This clinical overview is based on published scientific literature. A worldwide scientific and medical literature search was performed using the whole spectrum of bibliographic databases, including Embase and MEDLINE. The abstracts or full-texts of the retrieved publications were reviewed for their relevance to clinical overview. Whenever necessary, the reference lists of original publications were searched for complementary publications manually.

IV.2 Pharmacokinetics

Following oral administration, the absorption kinetics of salicylate in humans follow a first-order process, with 68% of the ASA dose reaching the systemic circulation unhydrolysed. ASA is rapidly hydrolysed to salicylic acid in the intestine wall and the liver, with a short elimination half-life of 15 to 20 minutes, corresponding to the increase of plasma salicylic acid.
Salicylic acid is normally highly protein bound (80 to 90%) at therapeutic plasma concentrations (1.1 to 2.2 mmol/L) and this probably accounts for the low reported values for the apparent volume of distribution, which range between 9.6 and 12.7 L in adults and between 0.12 and 0.14 L/kg in children. ASA is hydrolysed by nonspecific esterases to salicylic acid in gastric and intestinal mucosa, liver, plasma and other body tissues.
The elimination of salicylic acid is more complex and it is removed from the body by 5 parallel and competing pathways; 1 renal and 4 metabolic.

IV.3 Pharmacodynamics

ASA inhibits the biosynthesis of prostaglandins via irreversible blockade of cyclooxygenase (COX) activity by acetylating the serine 530, present in the active site of the enzyme. Consequently, the oxidative conversion of arachidonic acid to PGG and PGH is prevented, resulting into anti-inflammatory, analgesic and antipyretic effects of ASA.

IV.4 Clinical efficacy

Unstable angina pectoris
The indication has been proven by submitting 3 main studies: 1 multicentre, double-blind, placebo-controlled randomised trial and 2 randomised, double-blind, placebo-controlled trials.

Acute myocardial infarction and prevention of re-infarction
The role of ASA in reducing cardiovascular disease mortality and repent events after acute myocardial infarction was first demonstrated in the ISIS-2 trial.

Prevention of transient ischemic attack or cerebral infarction after previous sign:
The Swedish ASA Low-dose Trial (SALT) investigated the efficacy of 75 mg ASA daily in the prevention of stroke and death after TIA or minor stroke.

Treatment after surgery or other interventions on arterial vessels:
2 controlled trials have shown protection of early arterial graft occlusions by low-dose ASA pre-treatment.

Considering the proposed indications, use of ASA in adults for the treatment of unstable *angina pectoris,* acute myocardial infarction, prevention of re-infarction, prevention of TIA or cerebral

infarction after previous signs and after surgery or other interventions on arterial vessels was sufficiently documented.

IV.5 Clinical safety

As adverse effects following conditions were discussed in clinical overview: haemorrhage and blood disorders, intracranial haemorrhage, gastrointestinal toxicity, hypersensitivity and skin reactions, renal effects, liver impairment.

Elderly
ASA is frequently used in the elderly as single medication or in combination with other drugs. In the elderly, drug clearance may be retarded eventually resulting in toxic symptoms specifically in long-term use for prevention. At conventional antiplatelet doses, the risk of ASA overdosing is low.

Pregnant and lactating women
Low doses (up to 100 mg/day):
Clinical studies indicate that doses up to 100 mg/day for restricted obstetrical use, which require specialised monitoring, appear safe.

Doses of 100-500 mg/day and above
During the first and second trimester of pregnancy, acetylsalicylic acid should not be used unless clearly necessary. If acetylsalicylic acid is used by a woman attemping to concieve, or during the first and second trimester of pregnancy, the dose should be kept low and duration of treatment as short as possible.
During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to: cardiopulmonary toxicity and renal dysfunction.
At the end of pregnancy, all prostaglandin synthesis inhibitors may expose mother and child to: possible prolongation of bleeding time, an antiaggregating effect which may occur even at very low doses, inhibition of uterine contractions resulting in delayed or prolonged labour.

Breast-feeding
Low quantities of salicylates and their metabolites are excreted into the breast milk.

Patients with other co-morbidity
Hepatic impairment
Generally, ASA-induced liver injury develops after one to four weeks' treatment with relatively large doses of ASA, where in most cases it is mild and reversible.

Gout
Use of low-dose ASA is associated with a higher risk of recurrent gout attacks.

Safety in glucose-6-phosphate dehydrogenase deficient individuals
Among other drugs, ASA has been linked to acute haemolysis in glucose-6-phosphate dehydrogenase (G6PD)-deficient individuals.

Contraindications
ASA is contraindicated in persons with active, or a history of recurrent peptic ulcer and/or gastric/intestinal haemorrhage, or other kinds of bleeding such as cerebrovascular haemorrhages. ASA is contraindicated in persons with haemorrhagic diathesis or coagulation disorders such as haemophilia and thrombocytopaenia. ASA is contraindicated in persons who are suffering from gout. ASA is contraindicated in persons with severe hepatic or renal impairment. Doses of ASA higher than 100 mg per day during the third semester of pregnancy are contraindicated. ASA is further contraindicated in patients using methotrexate, patients suffering from gout and coagulation disorders.

Overdose
Generally, in adults, plasma salicylate concentrations between 150-300 mg/kg are associated with mild to moderate toxicity and concentrations in excess of 300 mg/kg confirm severe poisoning. The acute

fatal dose of ASA in adults has been estimated at 500 mg/kg. In the early stages of moderate to severe salicylate poisoning, nausea, vomiting, sweating, epigastric pain, flushing, vasodilatation, tremor, hyperventilation, tinnitus, and deafness may all occur. Hearing loss is completely reversible within two or three days after withdrawal of the drug and tinnitus does not occur in patients with pre-existing hearing loss.

IV.6 Risk Management Plan

The MAH submitted a risk management plan version number 1.1 signed 17/08/2017 with data lock point for this RMP 30/10/2016, 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 Kyselina acetylsalicylová Xantis 100 mg tablets.

Safety specification

Important identified risks	• Haemorrhage (including intracranial haemorrhage) • Hypersensitivity reactions • Gastrointestinal toxicity • Severe skin reactions (including Steven-Johnsons syndrome and toxic epidermal necrolysis) • Deterioration of renal function • Liver impairment • Drug interactions • Use in the third trimester of pregnancy
Important potential risks	• Reye's syndrome • Lactation • Use in the first and second trimester of pregnancy
Missing information	• None

Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

V. USER CONSULTATION

The package leaflet 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 language used for the purpose of user testing the PIL was English.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The user testing of 22 tested subjects showed that all participants were able to find the correct section and gave the correct answer.
The main negative aspect raised by several participants was the leaflet containing too much information. However, as the leaflet accurately presents its SmPC and all the corresponding key safety issues for the patient, the leaflet cannot be simplified further without losing some of the key safety

messages. Moreover, a lot of the participants mentioned informativeness of the leaflet as a positive aspect.

In RMS opinion submitted PL contains all information stated in SmPC. It is also comparable with PL of other medicinal products containing acetylsalicylic acid as an active substance that are authorised in SK. The final PL met the needs of the patients and it enabled to use the medicinal product safely and effectively.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The benefit risk assessment was considered positive. Therefore the RMS recommended approval of Kyselina acetylsalicylová Xantis 100 mg, tablets.