The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use

London, 25 July 2002
Doc. Ref: EMEA/CPMP/EWP/282/02/Final

POSITION PAPER ON THE REGULATORY REQUIREMENTS FOR THE AUTHORISATION OF LOW-DOSE MODIFIED RELEASE ASA FORMULATIONS IN THE SECONDARY PREVENTION OF CARDIOVASCULAR EVENTS

1. INTRODUCTION

This Position Paper focuses on the prerequisites for approval of new low-dose oral Modified Release (MR)-formulations of acetylic salicylic acid (ASA) in the well-established indication of secondary prevention of cardiovascular events (i.e. after first ischaemic stroke or myocardial infarction).

For a new MR-formulation no traditional bioequivalence in terms of pharmacokinetics can be demonstrated because of the differences in plasma concentration time course of ASA and its metabolite salicylic acid (SA) between an Immediate Release (IR) and a MR formulation. In addition, any widely acknowledged MR-reference product is lacking.

For applications for a new MR-formulation of a drug that is currently authorised as an IR formulation the relevant EU-"Note for Guidance on Modified Release Oral and Transdermal Dosage Forms: Section II (Pharmacokinetic and Clinical Evaluation)" states that

"In general it will be necessary to carry out controlled clinical trials", especially in cases where "the existence of equivalent levels of effect to those obtained with the IR form cannot be assumed on the basis of PK or PD data alone".

So far, all valid clinical studies proving the efficacy and safety of ASA for secondary prevention of cardiovascular events have been performed using immediate release formulations of ASA. Efficacy of IR-ASA in secondary prevention of cardiovascular events was convincingly shown in large-scale clinical trials and the antithrombotic effect does not seem to be dose-dependent. Therefore, a relatively wide dose range was recommended internationally, i.e. 75 to 325 mg in cardiology.

From a regulatory perspective there is a concern that a potential difference in efficacy between MR-ASA and IR-ASA - for which a substantial benefit in secondary prevention has been proven - cannot be excluded. There is a risk of withholding patients an effective and safe anti-thrombotic therapy.

As a consequence, the basis for approval of a new MR-ASA formulation has to be defined, in particular whether clinical data were needed and what kind of data will be sufficient.

In the absence of sufficient efficacy/safety data for the MR-formulation, the question arises whether it might be possible to grant a marketing authorisation for a new MR-formulation on the basis of proven pharmacodynamic equivalence.

2. SCIENTIFIC BACKGROUND

2. 1. The surrogate value of the reduction of thromboxane B_2 concentration

Currently, the reduction of thromboxane B_2 levels in serum (not in plasma) can be considered as a widely accepted surrogate for platelet aggregation and also for efficacy in secondary prevention of CV events. However, it should be clearly stated that thromboxane B_2 is a surrogate marker, and has never been validated by measuring TXB_2 simultaneously with assessment of clinical endpoints. Although there is no study showing a clear link between secondary prevention of cardiovascular events by ASA and reduction of thromboxane B_2 concentration, it can be agreed upon that this surrogate parameter

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reflects a major mechanism of action of ASA and that there is a correlation to effects on clinical outcome (cf. ICH-E9, requirements for surrogate variables). This is supported by the following evidence:

There is strong evidence that the thromboxane mechanism is the main mechanism of action of ASA and captures the whole net effect of ASA.

ASA has been reported to have effects on haemostasis that are unrelated to its ability to inactivate platelet COX-1. These include dose-dependent inhibition of platelet function, enhancement of fibrinolysis and suppression of plasma coagulation. The putative mechanisms underpinning the nonprostaglandin effects of ASA on haemostasis are dose-dependent and less clearly defined. The evidence of other mechanisms of the inhibition of platelet function by ASA (or SA) was considered to be very weak. Although there is some evidence from in vitro experiments and in vivo studies that ASA may inhibit platelet function by a mechanism that is unrelated to the inhibition of TXA_2 synthesis, the results of clinical trials, in which different doses (ranging from 75 to 1500 mg/day) have been used, are consistent with the hypothesis that the antithrombotic effect of ASA is caused by the inhibition of platelet TXA_2 synthesis.

The clinical effects cannot be explained sufficiently by assuming another, thromboxane-independent, mechanism of action.

Additional (extra-platelet) effects were found with higher concentrations of ASA (indicating dose-dependency). If these would be important, there should be a dose-response relationship and higher doses should be more effective (greater risk reduction for CV events). However, no further protection was afforded by 20 fold higher doses of ASA (than the lower limits of the range, i.e. 75 mg in cardiology).

The characteristics of the effects demonstrated by IR-ASA (effect at low doses 75-160 mg, given once daily – despite the very short half-life of ASA, i.e. a clear-cut dissociation between PK and PD) give support for the thromboxane-mediated mechanism of platelet aggregation inhibition. This is supported by clinical trial data.

The evidence suggesting dose-dependent effects of ASA is indirect and is inconsistent with the failure to show a dose effect in randomised clinical trials and in the overview analysis of the Antithrombotic trials. This failure to show a dose effect correlates with the saturability of the ASA effect on platelet COX-1. When the dose of ASA was raised, no further or additional benefit can be appreciated because the critical event has already taken place, namely the maximal inhibition of platelet TXA_2 synthesis.

Thus, the consistency of dose requirements and saturability of the effects of ASA in acetylating the platelet enzyme, inhibiting TXA_2 production and preventing atherothrombotic complications constitute the best evidence that ASA prevents thrombosis through the inhibition of TXA_2 production.

It can be concluded that other mechanisms of action do not add additional benefit and therefore, do not appear to be important for the efficacy in secondary prevention of CV events.

2.2. The role of the major metabolite of ASA, namely SA, for efficacy in prevention of CV events

According to current knowledge, the metabolite SA does not appear to contribute to thromboxane synthesis or inhibition of platelet aggregation.

However, the role of SA should be considered and critically discussed since there are substantial differences between IR and MR-formulations regarding the release pattern and consequently the plasma time course of ASA and SA. A potential effect of SA can be more pronounced with MR-formulation as compared to IR-form since - in contrast to the IR-form - the MR form produces constantly higher plasma levels of SA.

SA was described to interact also with the COX at an additional binding site (Arg 120, different from the catalytic site), thereby preventing binding of ASA and thus, inhibition of thromboxane synthesis. Consequently, it may antagonise the effect of ASA on COX.

However, in case of a modifying effect of SA (antagonising the cyclooxigenase inhibiting effect of ASA) this is likely to be detected by measurement of thromboxane levels (serial measurements at different time points). Consequently, this concern regarding a potential influence of SA on the effect

of ASA with the MR-formulation will be addressed by sound demonstration of PD-equivalence (in case of a relevant effect of SA the demonstration of equivalence would be unlikely).

Furthermore, in order to investigate the effect of SA or other anti-inflammatory agents (known to influence the effect of ASA) additional interaction studies with other anti-inflammatory agents may become necessary.

3. REQUIREMENTS FOR THE AUTHORISATION OF A NEW MR-ASA FORMULATION IN THE SECONDARY PREVENTION OF CARDIOVASCULAR EVENTS

According to the Note for Guidance (NfG) on Modified Release formulations the development of a new prolonged or delayed release formulation should be "based on a well-defined clinical need and on integration of physiological, pharmacodynamic and pharmacokinetic considerations" (section 2.1 of the NfG). Furthermore, a complete justification should be provided (among others) for "the clinical relevance of the new form particularly in relation to the proposed indications and posology." The scientific rationale should be provided and discussed by the Applicant.

In case the Applicant claims any advantages for the low-dose MR-ASA formulation over immediate release (IR) ASA with respect to efficacy and/or safety, this should be proven by a controlled clinical trial with hard clinical endpoints. Even if no advantage is claimed, it has to be reassured that there are no safety concerns related to bleeding/ulceration with the MR formulation compared to IR formulation. Any claim regarding superiority in safety will require a clinical safety study to prove this.

However, at present, any advantage of MR-formulations in terms of efficacy or safety cannot be seen in view of the following:

a) The antiplatelet effect of ASA is largely independent of the systemic bioavailability, since the platelet COX-1 is acetylated in the pre-systemic circulation. All IR-ASA formulations are long-acting and administered once daily, since the effect on the platelet is irreversible and lasts for the life-span of the platelet (up to 10 days).

b) In terms of efficacy it should be ensured that the new MR-formulation is not inferior to IR-ASA. The theoretical approach to improve the efficacy by minimising the impact of ASA on prostacyclin synthesis (a vasodilator and antiaggregant) remains to be clinically proven. There is only one placebo-controlled trial of a MR-form in primary prevention, which showed no difference between MR-ASA and placebo regarding the combined clinical endpoint (all ischaemic heart disease, i.e. coronary death and fatal and non-fatal MI). The demonstration of a small additional benefit (if one can be expected) requires a big trial, which is unlikely to be feasible.

c) In terms of safety there may be an expectation that the haemorrhagic risk (in particular serious gastrointestinal (GI) bleedings) can be reduced. However, since this risk is intrinsically related to the antiplatelet effect, which appeared not to be dose-related, this seems unlikely. According to clinical data, ASA in the dose range of 75-100 mg increases the risk of bleeding (from pre-existing lesions) in the upper GI-tract with a relative risk of 2.

Any advantage in terms of improvement of gastric tolerance is considered to be difficult to demonstrate. There is a high level of "noise" (approx. 20-25% of patients on placebo report symptoms) and the clinical relevance of probable reduction of e.g. dyspeptic symptoms is unclear. Furthermore, long-term repeated endoscopy studies are not considered appropriate since the clinical relevance of those findings is questionable (results do not translate into serious complications). Serious outcomes such as bleedings (leading to hospitalisation) and perforations etc. are more relevant and therefore, in order to show an improvement of gastric tolerance, a large clinical study with such endpoints would have to be performed.

Moreover, an additional concern has to be addressed with respect to the MR formulation, namely its potential risk of inducing ulcers in the small bowel, which are not seen with IR-ASA.

In addition to an appropriate justification of the new low-dose MR-ASA formulation the following requirements for the approval in the secondary prevention indication can be summarised:

1. If the Applicant intends any specific claim supplementary to the labelling of the IR-formulation for the MR-formulation (e.g. an advantage of the MR-formulation over the IR-ASA formulation either with respect to efficacy and/or safety), this should be proven in large clinical trial(s) with clinical endpoints (CV events).

2. Only in the case of an application not highlighting any specific claims – the demonstration of pharmacodynamic equivalence / non-inferiority using the surrogate parameter thromboxane B_2 levels – measured in serum - will be sufficient to grant the indication secondary prevention of cardiovascular events.

Solid and robust evidence indicating equivalence /non-inferiority regarding TXB_2 levels should be presented. Pharmacodynamic equivalence based on thromboxane B_2 kinetics (tmax, maximal % of inhibition and AUC as well) should be assessed after single as well as repeated doses in a sufficient population of both healthy volunteers (at least approx. 40) and patients (number to be determined and justified by the applicant) to allow the detection of possible resistances or non-responders. The power of the statistical comparisons justifying sample sizes should be discussed.

The comparison should be made with a standard dose of IR-formulation (in the approved dose range). The minimal effective dose (based on clinical criteria), which could be used as reference in this demonstration should definitively not be less than 75 mg IR-ASA per day.

In general, based on safety grounds, the dose of the experimental product should not be higher than that of the IR-ASA comparator.

Thromboxane levels should be measured in serum using a standardised procedure and a validated assay method. Serial measurements of thromboxane are necessary in order to describe (and show equivalence regarding) the time course of thromboxane inhibition. The pharmacodynamic equivalence should be assessed on a high number of samples covering the 24-hour period.

A high percentage of inhibition of thromboxane B_2 synthesis (close to 100% inhibition) should be achieved to show non-inferiority. In addition, the percentage of subjects being "responders" (i.e. achieving this threshold) should be determined as an additional (secondary) parameter. The chosen limits of equivalence should be pre-defined and adequately justified by the Applicant in view of their clinical relevance. It should be noted, that the equivalence limits usually accepted for demonstration of pharmacokinetic bioequivalence (± 20%) are considered too wide for the surrogate pharmacodynamic parameter thromboxane B_2 levels.

3. If the PD equivalence could be convincingly demonstrated, it should be clearly mentioned in the SPC (preferably section 5.1 – PD properties) that

- the approval was based on surrogate markers (namely inhibition of thromboxane B_2 synthesis) and
- there is no clinical data comparing the MR formulation with an IR-form with respect to clinical outcome.

4. In addition, the claimed indication (section 4.1 of the SPC) should clearly state, that the MR formulation is not suitable for patients in acute situations since the onset of the platelet inhibiting effects is considerably delayed as compared to the IR- form.

There is consensus, that in clinical situations where an immediate antithrombotic effect is required (such as acute MI, acute ischaemic stroke, unstable angina) a loading dose of about 150 - 300 mg of IR-ASA should be given.

In conclusion, a formal guarantee that MR- low-dose ASA is equally effective as low-dose IR-ASA cannot be given. However, a robust and convincing demonstration of PD equivalence with respect to TXB_2 should give sufficient assurance that the new MR formulation will be equally effective in secondary prevention of CV events.