31 May 2018
EMA/CHMP/644911/2017
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Prasugrel hydrochloride film-coated tablets 5 mg and 10 mg product-specific bioequivalence guidance' (EMA/CHMP/158772/2016/Rev.1)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	Alembic Pharmaceuticals Limited
2	European Association of Hospital Pharmacists (EAHP)
3	Zentiva, k.s., Czech Republic
4	Sanofi generics
5	PharOS Ltd

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
2	EAHP supports the additional requirements for bioequivalence demonstration.	
4	Specific product guidance is considered as a significant step further in cultivating regulatory environment. If it is released around the time of patent / data exclusivity expiry it still brings value to the regulator and industry as it represents solid ground for discussion during registration procedure. Unfortunately, it does not help the public health since it brings additional requirements that are difficult to predict too late. Then, there is lower number of generic products reaching the market resulting in less competition. This is partly related to the statistical chance / power of the additional study and sadly not the product quality. We are of the opinion, that product specific guidance has significant potential to bring great value to the public health as well as to the regulators and industry if released on time. That is just after the original product approval.	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
26 - Bioequivalence study design	1	Comment: The BE study design in the draft guidance mentions the following: *"An additional study under fed conditions is recommended if the generic product contains a different salt form than the originator or the free base of prasugrel".* Prasugrel is indicated for the prevention of atherothrombotic events in adult patients with acute coronary syndrome (i.e. unstable angina, non-ST segment elevation myocardial infarction [UA/NSTEMI] or ST segment elevation myocardial infarction [STEMI]) undergoing primary or delayed percutaneous coronary intervention (PCI). As the PCI is usually performed in the fasted state, the food effect may not be clinically relevant. Accordingly, dosing recommendation in the reference product SPC given as "administration of the 60 mg prasugrel loading dose in the fasted state may provide most rapid onset of action". As per the EMA guidance: CPMP/EWP/QWP/1401/98, a bioequivalence study should be conducted under fasting conditions as this is considered to be the most sensitive condition to detect a potential difference between formulations. Hence, the bioequivalence study in fasting condition suffices the requirement to prove bioequivalence since the SPC of the reference medicinal product recommends intake to take with or without food.	Not accepted. According to the SmPC of the originator, the product may be administered with or without food. Since the solubility is different among different salt forms or the free base of prasugrel an additional study under conditions of elevated gastric pH i.e. fed or pre-treated with a PPI conditions is recommended to demonstrate that the formulations are affected in the same way by concomitant food intake, unless scientifically justified i.e. considering solubility, dissolution and formulation.

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		According to the earlier adopted guidance (doc. Ref. EMA/CHMP/158772/2016), the parent compound is not detected in human or animal plasma (or other biological matrix) and hence bioequivalence should be based on the first metabolite, R-95913. Here whether the drug substance is in different salt form or free base than the originator, the bio-equivalence should be based on 90% Confidence Intervals of first metabolite R-959013. Based on the above justification, we believe that the requirement for bioequivalence under fed conditions should be waived with a different salt form or the free base.	
26 - Bioequivalence study design	3	Comment: The draft guideline for Prasugrel products states that an additional study under fed conditions is recommended if the generic product contains a different salt form than the originator or the free base of prasugrel. However, the physical/chemical characteristics of different alternative salts of Prasugrel can differ significantly and therefore the risk of significantly different pharmacokinetic profiles in fed state should be evaluated individually for each particular alternative salt of Prasugrel. The parameters that should be taken into consideration should be alternative salt solubility and API release from the drug product. Gastric pH in fed state is higher than in fasted state, but dissolution experiments in pH higher than 3 are	Partly accepted. It is acknowledged that the physical/chemical characteristics of different alternative salts of prasugrel can differ significantly and therefore the risk of significantly different pharmacokinetic profiles under conditions of elevated gastric pH (i.e. fed or pre-treated with a PPI) should be evaluated individually for each particular alternative salt of prasugrel. The guideline has been amended to reflect this with the addition of a statement that the additional study under conditions of elevated gastric pH is recommended unless scientifically justified i.e. considering solubility, dissolution and formulation.

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		increasingly limited by the solubility of Prasugrel and its salts (due to a sharp solubility decrease around its pKa of 5.1) Therefore, any differences between various Prasugrel formulations seen in such media (including FeSSIF) are not biorelevant. Clinical irrelevance of such in vitro experiments is also is due to the lipophilicity of Prasugrel (LogP 4.3). There may be differences in dissolution of Prasugrel hydrochloride and alternative salt products at pH higher than 3, but in the scenario of a fed state study, soluble Prasugrel will preferentially migrate into the lipidic fraction enabling the solubilisation of the remainder of API. This would result in a bioequivalency of both formulations. In conclusion, if the alterantive salt product was bioequivalent to the prasugrel hydrochloride product in fasted conditions, displays similar release properties in dissolution in low pH media (pH1.2 or 2) and similar disintegration, there is no reason to expose additional subjects to further clinical testing in a fed state study. Proposed change: An additional study under fed conditions is recommended if the generic product contains a different salt form than the originator or the free base of prasugrel, **if the generic product exhibits significantly different API release properties in dissolution experiments in media with low pH (pH 1.2 or 2) or significantly different**	

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		disintegration properties.	
26 - Bioequivalence study design	4	Comment: It is well described in the Efient EPAR: “Clinical studies have demonstrated that tablet performance is not affected by formation of the free base over a range of 5%-70% conversion. AUC and Cmax of the active metabolite were bioequivalent after 1 hour. Regulatory consistency on the requirements on all applications containing prasugrel in different forms would be appreciated. If the physical/chemical characteristics of different alternative salts of prasugrel differ less than the one of the prasugrel base then the plasma concentration of the active metabolite is similar to Efient market image and well in the range of the Eli Lilly clinical supply to clinical phase III study. In this situation fed study is not expected to bring additional value and could be reasonably waived. Proposed change: **If the alternative salt differs in physical/chemical characteristics more than prasugrel base compared to the prasugrel hydrochloride, an additional study under fed conditions is recommended.**	Partly accepted. It is acknowledged that the physical/chemical characteristics of different alternative salts of prasugrel can differ significantly and therefore the risk of significantly different pharmacokinetic profiles under conditions of elevated gastric pH (i.e. fed or pre-treated with a PPI) should be evaluated individually for each particular alternative salt of prasugrel. The guideline has been amended to reflect this with the addition of a statement that the additional study under conditions of elevated gastric pH is recommended unless scientifically justified i.e. considering solubility and dissolution and formulation.
12-14 and 26	5	Comment: As per product specific bioequivalence guideline on Prasugrel Hydrochloride, one fasting study on the highest strength is	Not accepted. A study under fed or pre-treated with a PPI conditions is considered sufficient to demonstrate bioequivalence

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		considered enough for bioequivalence demonstration. Bioequivalence should be based on the first metabolite, R-95913. Within the same guideline an additional study under fed conditions is recommended if the generic product contains a different salt form than the originator or the free base of prasugrel. Prasugrel is an inhibitor of platelet activation and aggregation through the irreversible binding of its active metabolite to the P2Y12 class of ADP receptors on platelets. Since platelets participate in the initiation and/or evolution of thrombotic complications of atherosclerotic disease, inhibition of platelet function can result in the reduction of the rate of cardiovascular events such as death, myocardial infarction, or stroke. As per Efient's SPmCi, prasugrel HCl is co-administered with acetylsalicylic acid (ASA), for the prevention of atherothrombotic events in adult patients with acute coronary syndrome (i.e. unstable angina, non-ST segment elevation myocardial infarction [UA/NSTEMI] or ST segment elevation myocardial infarction [STEMI]) undergoing primary or delayed percutaneous coronary intervention (PCI). As such it can also be concomitantly administered with medicinal products that elevate gastric pH, including proton pump inhibitors, as per common medical practice in patients taking low-dose aspirin on the risks of adverse gastrointestinal (GI) events.	under conditions of elevated gastric pH.

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		As per published innovator's dataii Prasugrel development began with prasugrel base, which was used in the earlier clinical studies in healthy subjects and subjects with stable atherosclerosis. Although initial studiesiii had demonstrated that tablet performance was not affected by formation of the free base over a range of 5%-70% with regards to conversion as AUC and Cmax of the active metabolite were bioequivalent after 1 hour, this was not the case when administered in the presence of concomitant treatment with proton pump inhibitors (PPIs) or H2-receptor antagonists which raise gastric pH. Relevant clinical studies in this case showed that the Cmax and AUC of prasugrel's inactive metabolites were substantially reduced when prasugrel base was given to healthy subjects whose gastric pH was >6 at the time of dosing. More specifically, as per innovators data two bioequivalence studies were conducted, comparing the bioavailability of lots with low (5%), intermediate (58%), and high (70%) degrees of conversion to base, with and without co-administration of a PPI (lansoprazole) to raise gastric pH. From this study it was found that: • When prasugrel 60-mg was administered without a PPI, Prasugrel lots with low, intermediate, and high salt to base conversion were bioequivalent with respect to R-138727, prasugrel's active moiety for both Cmax and area under the curve (AUC).	

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		• When prasugrel 60-mg was administered on a background of lansoprazole Prasugrel lots with low, intermediate, and high salt to base conversion were still bioequivalent for R-138727 with respect to AUC, but were not bio-equivalent with respect to Cmax (Table 1). The mean difference in Cmax between the low and the high conversion lots was 29% (90% confidence interval [C.I.] 17%, 38%), and there was a 20% difference in Cmax between the medium and high conversion lots (90% C.I. 8%, 31%). **Table 1:** Relative Bioavailability of R-138727, the Active Moiety of Prasugrel-Comparison of Low, Medium, and High Extends of Conversion with Background 30-mg Lansoprazole	

Geometric least square means (90% CI)			Ratio of means (90% CI)		
Prasugrel-LC	**Prasugrel-MC**	**Prasugrel-HC**	**M-C/LC**	**H-C/L-C**	**H-C/M-C**
AUC(0-t_{last}) (ng.h/mL)					
470 (424, 522)	467 (421, 518)	409 (368, 454)	0,99 (0.93, 1.06)	0,87 (0.82, 0.93)	0,88 (0.82, 0.93)
C_{max} (ng/mL)					
331 (285, 384)	297 (257, 344)	236 (204, 274)	0,90 (0.77, 1.04)	0,71 (0.62, 0.83)	0,80 (0.69, 0.92)

LC=Low conversion; MC=Medium conversion; HC=High conversion

Analysis of the pharmacodynamics of prasugrel in the presence and absence of PPI provides insight into the potential consequences of these differences in Cmax. The effects of thienopyridines on platelet aggregation last for the life of a platelet and are concentration dependent. A delay in

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		reaching Cmax, i.e., a lengthened Tmax or a lower Cmax, could delay the full effect of the drug on platelet aggregation. Especially for the 60-mg prasugrel loading dose, these differences translated into absolute disparities in inhibition of platelet aggregation (IPA) of approximately 20% at 0.5 hours post-dose (high versus low- or medium-salt-to-base conversion) and 12% at 1 hour post-dose, when prasugrel is given on a background of lansoprazole (Figure 2). Thus, at the time points that bracket Tmax, the high salt-to-base conversion lots are not bio-equivalent to lots with medium or low conversion. However, at subsequent time points (2, 4, and 24 hours post-dose), inhibition of platelet aggregation continued to increase, such that IPA was virtually identical with lots of all degrees of conversion by two hours. In essence, therefore, the bioinequivalence results in a delay of perhaps 20 minutes in achieving maximal inhibition of platelet aggregation. This is manifested only with the high salt-to-base conversion product, and only in the presence of PPI or H2 receptor antagonists. Because percutaneous coronary intervention (PCI) may precipitate periprocedural myocardial infarction, a considerable number of events occur very soon after PCI. As a case in point, in an innovator's pivotal efficacy study (TAAL), of all the non-fatal myocardial infarctions recorded during the course of the 15-month study, 30% of them occurred within the first hour of the study. Clearly, therefore, rapid inhibition of platelet aggregation may be important in preventing periprocedural nonfatal myocardial infarction (MI) and the delay in achieving inhibition of platelet aggregation resulting from use of the high salt-to-base conversion product in the presence of PPIs or H2 receptor blockers has at least the potential to be clinically meaningful.	

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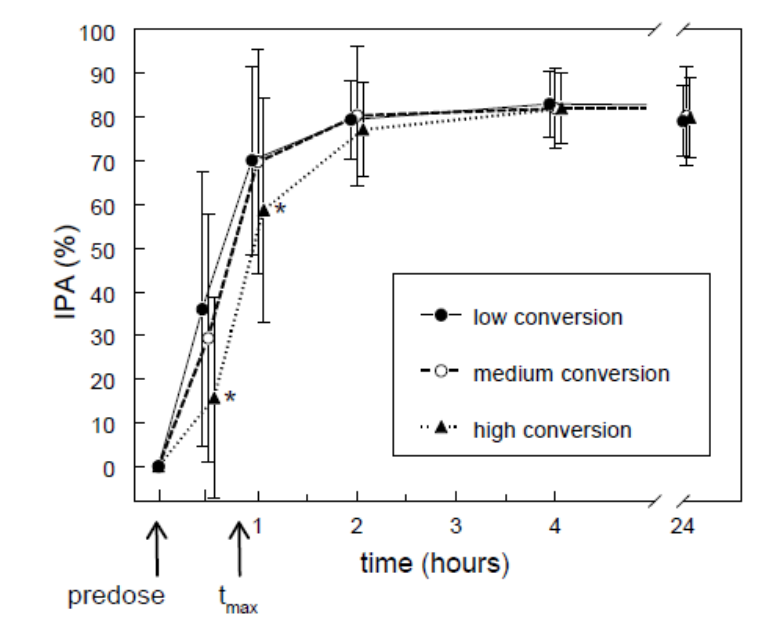
		Figure 1: Inhibition of Platelet Aggregation (IPA) to 20 µM ADP, following 60-mg Prasugrel: Lots with Low, Medium, and High Extents of Salt-to-Base Conversion on Background of Lansoprazole 30-mg (*p<0.01, high conversion versus low or medium conversion, mean ± SD; calculated by CDER, Study TACS)  Lansoprazole administration is sufficient to significantly decrease the basal acid output and significantly increase the mean gastric pH. More specifically, as per N.J.V BELL and R.H.HUNT[iv] publication the time to maximum inhibition of gastric acidity resulting from repeated oral dosing with lansoprazole 30 mg daily for 7 days was studied in nine	

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		healthy male volunteers. Twenty-four hour intragastric pH monitoring was performed before treatment and on days 1, 3, 5 and 7 of dosing with lansoprazole. Blood samples were taken for the estimation of plasma lansoprazole concentrations. Lansoprazole 30 mg increased mean 24-h intragastric pH to 3.57 on day 1 compared with baseline mean pH of 2.11 (P<0.05). The mean intragastric pH during the morning period (08.00-13.00 h) was significantly higher on days 3, 5 and 7 than on day 1, but no consistent differences between day 1, 3, 5 and 7 were noted for subsequent periods (13.00-18.00, 18.00-21.00 and 23.00-07.00 h). There were no differences in mean pH between days 3, 5 and 7. Concluding, Lansoprazole 30 mg raised intragastric pH significantly from baseline on day 1 to a maximum effect as early as 6 h after the first dose. Mean intragastric pH levels for lansoprazole 30mg by day of dosing are presented in figure 3, confirming that the highest gastric pH levels are reached approximately one hour after dosing and remain at their highest levels, close to pH 6 for approximately 2 more hours. **Figure 2:** Mean intragastric pH levels for lansoprazole 30mg by day of dosing.	

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		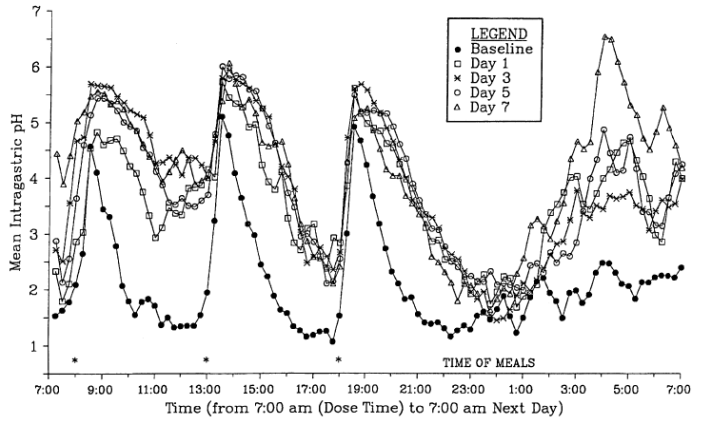 Eating can also increase intragastric pH at less extreme conditions and duration than what it is observed with PPIs. More specifically, from 1.3 to 2.5 range as observed in the fasting stage following food consumption intragastric pH is increased up to a 4.5 to 5.8 range, as per the below figure 4. Figure 4: Gastric pH in the fasted state and after food intake (pH6, 458 calories, and 400mL total volume) in 10 healthy volunteers (Malagelada and others 1976).	

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		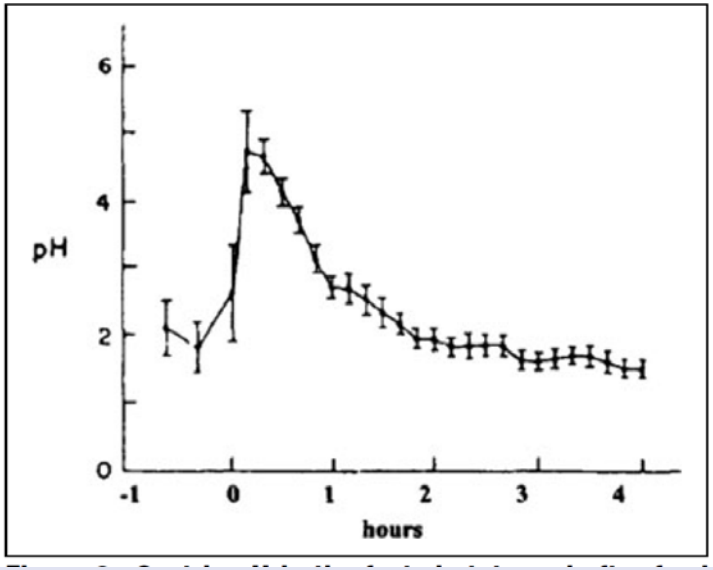 Solubility class boundaries are based on the highest dose strength of an immediate release product. More specifically, in accordance with the EMA bioequivalence guideline[iv], a drug is considered highly soluble if the highest single dose administered as immediate release formulation is completely dissolved in 250 ml of buffers within the range of pH 1 – 6.8 at 37±1°C. Comparative experimental data of a BCS solubility study conducted between Prasugrel Base and Prasugrel HCl, revealed the following results, as presented in table 2: **Table 2:** Comparative experimental data of a BCS solubility study between Prasugrel Base and Prasugrel HCl	

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	Results (mg Prasugrel/250mL medium)	
Media	**Prasugrel HCl**	**Prasugrel Base**
pH 1.2	2416.77	1286.98
pH 4.5	17.81	2.48
PH 6.8	0.89	0.47

From the above results it can be concluded that both prasugrel HCl and base are highly soluble at media with pH value of 1.2. At a higher pH of 4.5 only prasugrel HCl retains its classification as highly soluble, while prasugrel base is classified as a low solubility compound. Lastly, at the highest pH value of 6.8 revealed that both substances are classified as having low solubility.

Considering the gradually decreased solubility of prasugrel as the pH increases, reaching the lowest solubility point at the most extreme pH 6.8 condition, it can be concluded that although some formulation differences under low pH 1.2 conditions will be revealed, those will be even more exaggerated at higher pH values which practically reflects the most discriminative conditions in terms of solubility.

Moreover, solubility differences are known to be present not only between prasugrel HCL but also in the different prasugrel salts, known to have been used in the generic industry during the development of prasugrel generic immediate release formulations.

The decreasing solubility as pH increases mask formulation differences that could have been potentially captured from *in vitro* dissolution experiments. Therefore, provided also that Efient may be administered with or without food while

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		coadministration with PPIs is also recommended as per the relevant SmPC, one bioequivalence study under fasting conditions and one under fed as suggested by the EMA guideline[v] comparing prasugrel base or other salts different than HCl versus prasugrel HCl are not considered enough to show formulation differences in this case as an additional *in vivo* comparison under the most extreme gastric pH conditions in the presence of PPI is of mandatory importance to prove equivalence of the formulations. Proposed change (if any): In order to support a marketing authorization of a prasugrel base or different salt formulation in Europe, bioequivalence should be proven under the following conditions: 1) under fasting conditions in the presence of PPI, 2) under fasting conditions in the absence of PPI, 3) under fed conditions NOTE: The above suggestions is also in line with a scientific advice procedure submitted to EMA authorities within 2016 and concluded similarly with the suggestion of all 3 studies as described above.	

[i] https://www.medicines.org.uk/emc/medicine/21504
[ii] ASSESSMENT REPORT FOR Efient International Nonproprietary Name: prasugrel, Procedure No. EMEA/H/C/000984
[iii] FDA summary review on efient
[iv] N. J. V. BELL & R. H. HUNT, Time to maximum effect of lansoprazole on gastric pH in normal male volunteers, Aliment Pharmacol Ther. 1996; 10: 897±904.

[v] Prasugrel film-coated tablets 5 and 10 mg product-specific bioequivalence guidance*