LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Budaxiro
(budesonide)

SE/H/2359/01/DC

This module reflects the scientific discussion for the approval of Budaxiro. The procedure was finalised on 2024-02-15. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Budaxiro, 3 mg, Modified-release capsule, hard.

The active substance is budesonide. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Budaxiro, 3 mg, Modified-release capsule, hard, is a hybrid application submitted according to Article 10(3) of Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DE as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Entocort®, 3 mg, Modified-release capsule, hard authorised in Sweden since 1995, with Tillotts Pharma GmbH as marketing authorisation holder.

The reference product used in the bioequivalence studies is Entocord, 3 mg, Modified-release capsule, hard from Spain with Tillotts Pharma GmbH as marketing authorisation holder.

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of budesonide are well known. As budesonide is a widely used, well-known active substance, no further studies are required, and the applicant provides none. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Upon request the applicant has provided with budesonide consumption data over the last 5 years. In Sweden (RMS) the consumption has decreased with -20.1% while in Germany (CMS) the consumption has increased with 5.6% which is similar to the total increase in EU countries. This slight increase is within acceptable limits and since Budaxiro is a generic product, the environmental exposure to the drug substance is not expected to increase significantly.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted two single-dose bioequivalence studies comparing Budaxiro (Budesonide) with the reference product Entocord in fasting and fed conditions and a *post hoc* sensitivity analysis of different partial AUCs from the performed studies.

Pharmacokinetic properties of the active substance
Absorption: After oral dosing of plain micronised budesonide, absorption is rapid and seems to be complete. A large proportion of the drug is absorbed from the ileum and ascending colon. In patients with active Crohn's disease systemic availability is approximately 12-20% after a single-dose. Systemic availability in healthy subjects is approximately 9-12%.

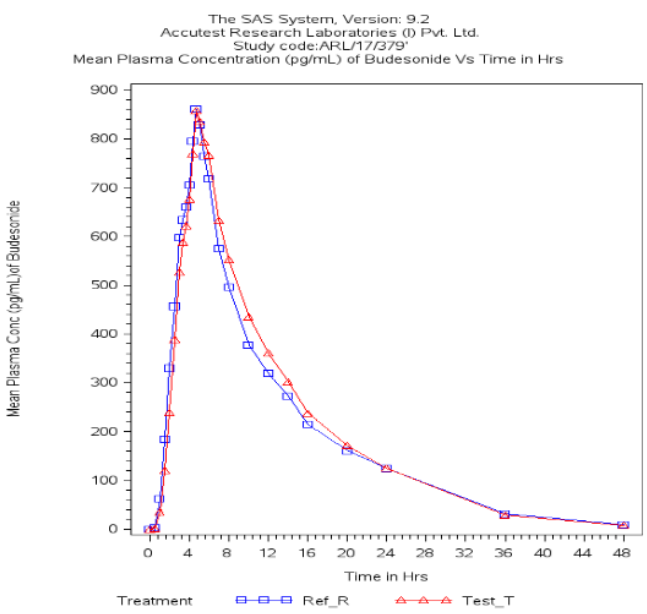
Elimination: Elimination is rate limited by absorption. The average terminal half-life is 4 hours. Budesonide has a high systemic clearance (about 1.2 L/min).

Study ARL/17/379 – FASTING
Methods
This was a randomised, two-treatment, three-period, three-sequence single-dose, reference replicated crossover study conducted in 75 healthy volunteers, comparing Budesonide, 3 mg, enteric coated capsule with Entocord, 3 mg, modified-release capsule under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 48 hours post-dose. Plasma concentrations of budesonide were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for C_{max}, pAUCs (AUC_{0-4}, AUC_{4-t}), AUC_{0-t} and AUC_{0-inf}. The study was conducted between 16 December 2017 and 03 January 2018.

Results
The results are presented below.

Figure 1. Mean Concentration Time Profile-Un-tranformed & Log-transformed data for Budesonide

For Un-transformed data:



For Log-transformed data:

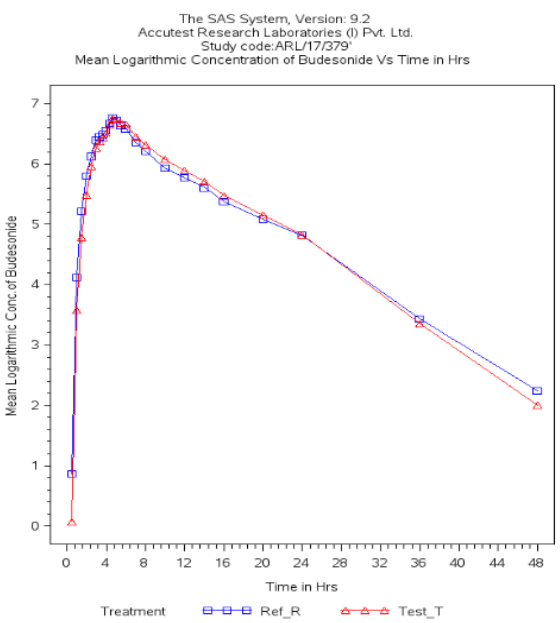


Table 1. Pharmacokinetic data of budesonide

Treat	N Obs	Variable	N	Mean	Std Dev	Coeff of Variation	Minimum	Maximum	Median
R	146	Cmax	146	955.245	581.307	60.854	236.044	4036.609	804.059
		Tmax	146	4.448	1.050	23.603	1.500	10.000	4.670
		AUC0_4	146	1310.007	995.477	75.990	20.947	5582.620	1096.561
		AUC4_t	146	7808.727	5145.139	65.890	977.376	39864.840	6467.493
		AUCt	146	9122.921	5686.186	62.329	1708.381	45447.460	7665.213
		AUC0_tau	146	8044.413	4712.023	58.575	1708.381	37051.552	6824.759
		AUCinf	146	9392.795	5803.035	61.782	1790.994	47385.412	7836.169
		Kele	146	0.109	0.027	25.133	0.043	0.191	0.107
		halflife	146	6.803	1.989	29.239	3.623	16.169	6.478
		Tlag	146	0.753	0.542	71.961	0.000	2.500	0.500
		AUCtaubyAUCinf_ratio	146	86.933	6.552	7.537	64.790	97.904	88.228
		AUC_ratio	146	96.631	3.459	3.579	68.389	99.519	97.658
		Residual_Area	146	3.369	3.459	102.655	0.481	31.611	2.342
T	74	Cmax	74	965.156	570.671	59.127	251.228	3560.329	799.828
		Tmax	74	4.874	0.943	19.355	3.000	10.000	4.670
		AUC0_4	74	1128.332	930.974	82.509	13.418	6277.231	1013.345
		AUC4_t	74	8303.843	4931.325	59.386	1783.977	29977.693	7256.438
		AUCt	74	9432.174	5528.044	58.608	2409.070	36254.924	8227.036
		AUC0_tau	74	8418.093	4662.608	55.388	2409.070	30260.798	7067.041
		AUCinf	74	9676.949	5601.638	57.886	2528.759	37334.066	8370.233
		Kele	74	0.118	0.024	20.128	0.054	0.167	0.115
		halflife	74	6.126	1.407	22.966	4.148	12.743	6.019
		Tlag	74	0.987	0.591	59.843	0.000	2.500	1.000
		AUCtaubyAUCinf_ratio	74	88.227	6.410	7.265	57.026	97.878	89.416
		AUC_ratio	74	96.990	2.759	2.845	87.132	99.487	97.928
		Residual_Area	74	3.010	2.759	91.664	0.513	12.868	2.072

Table 2. Bioequivalence evaluation (n=74)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref (%)	Confidence Intervals	Intra-CV (%)
C_{max}	100.8171	95.5087-106.4206	23.0173
AUC_{0-t}	103.2114	99.1603-107.4281	17.8813
AUC_{0-4}	88.8519	72.9612-108.2035	94.7819
AUC_{4-t}	106.9526	102.1074-112.0278	19.9557
AUC_{0-inf}	102.8128	98.8500-106.9343	18.0431
AUC_{0-12}	102.4292	98.0572-106.9962	18.0641

AUC_{12-t}	103.1428	96.4382-110.3135	29.8794

For AUC_{0-t}, AUC_{0-inf}, AUC_{4-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

For AUC_{0-4} the 90% confidence interval for the ratio of the test and reference products fell within the widened range of 69.84-143.19%.

Study ARL/17/380 – FED

Methods

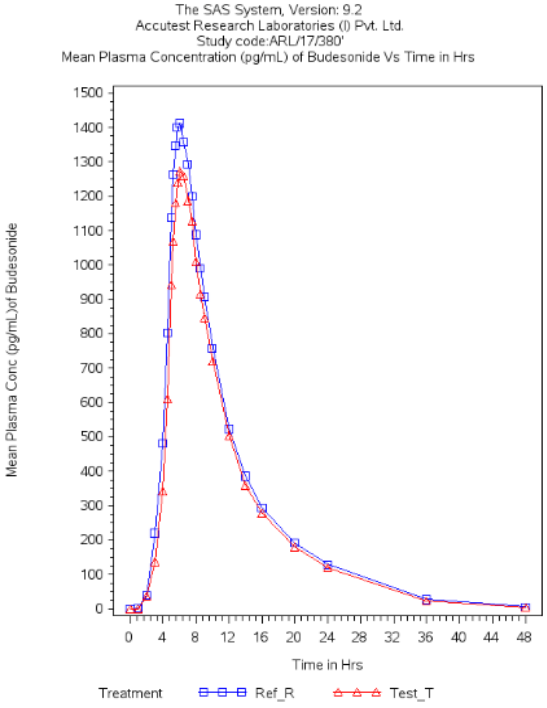
This was a randomised, two-treatment, three-period, three-sequence single-dose, reference replicated crossover study conducted in 75 healthy volunteers, comparing Budesonide, 3 mg, enteric coated capsule with Entocord, 3 mg, modified-release capsule under fed conditions. Blood samples for concentration analysis were collected pre-dose and up to 48 hours post-dose. Plasma concentrations of budesonide were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for C_{max}, pAUCs (AUC_{0-6}, AUC_{6-t}), AUC_{0-t} and AUC_{0-inf}. The study was conducted between 20 June 2018 and 11 July 2018.

Results

The results are presented below.

Figure 2. Mean Concentration Time Profile-Un-tranformed & Log-transformed data for Budesonide

For Un-transformed data:



For Log-transformed data:

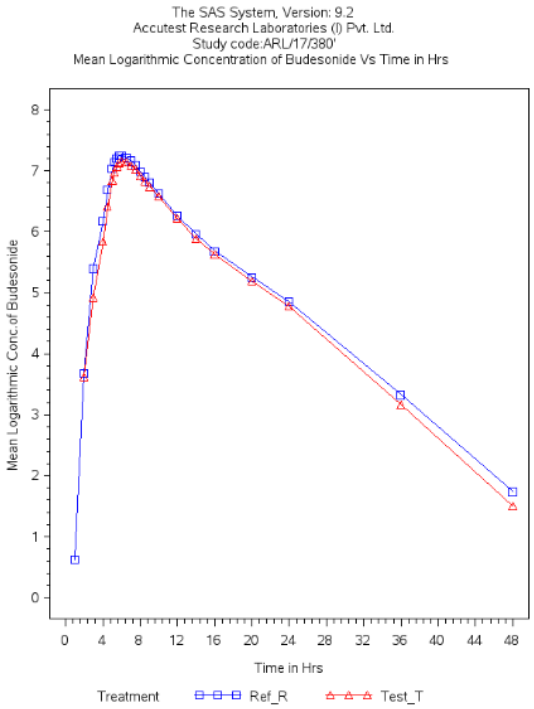


Table 3. Pharmacokinetic data of budesonide

Treat	N Obs	Variable	N	Mean	Std Dev	Coeff of Variation	Minimum	Maximum	Median
R	140	Cmax	140	1795.736	917.833	51.112	452.033	6346.958	1544.661
		Tmax	140	6.131	1.509	24.616	3.000	14.000	5.750
		AUC0_6	140	2631.155	2048.289	77.848	104.220	14719.530	2209.310
		AUC6_t	140	9856.645	6560.022	66.554	2502.005	47376.413	8405.295
		AUCt	140	12487.800	7361.147	58.947	3735.728	55857.829	10675.705
		AUC0_tau	140	11491.728	6230.689	54.219	3735.728	48218.370	10117.901
		AUCinf	140	12743.597	7410.124	58.148	3909.059	57017.563	11059.445
		Kele	140	0.123	0.023	18.781	0.067	0.207	0.120
		halflife	140	5.816	1.119	19.235	3.345	10.362	5.782
		Tlag	140	1.807	0.895	49.515	0.000	4.500	2.000
		AUCtaubyAUCinf_ratio	140	91.332	3.972	4.350	74.184	98.243	91.764
		AUC_ratio	140	97.497	2.538	2.603	81.450	99.519	98.402
		Residual_Area	140	2.503	2.538	101.403	0.481	18.550	1.598
T	68	Cmax	68	1673.403	746.112	44.586	387.091	3478.506	1513.936
		Tmax	68	6.798	2.114	31.091	4.000	16.000	6.500
		AUC0_6	68	2122.027	1815.363	85.549	101.783	7494.890	1685.658
		AUC6_t	68	9183.933	4915.997	53.528	2400.694	27704.812	8300.130
		AUCt	68	11305.960	5346.377	47.288	2878.540	29484.650	10363.376
		AUC0_tau	68	10420.952	4604.128	44.181	2878.540	25908.539	10053.100
		AUCinf	68	11549.995	5304.239	45.924	3084.176	29804.344	10663.947
		Kele	68	0.125	0.022	17.764	0.064	0.173	0.124
		halflife	68	5.737	1.143	19.924	4.012	10.878	5.592
		Tlag	68	2.354	1.054	44.787	1.000	4.500	2.000
		AUCtaubyAUCinf_ratio	68	90.921	4.283	4.710	70.164	96.254	91.871
		AUC_ratio	68	97.217	3.067	3.155	83.756	99.542	98.545
		Residual_Area	68	2.783	3.067	110.214	0.458	16.244	1.455

Table 4. Bioequivalence evaluation (n=68)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref (%)	Confidence Intervals	Intra-CV (%)
C_{max}	92.8462	87.0875-98.9858	25.6624
AUC_{0-t}	91.8696	87.6652-96.2756	20.5742
AUC_{0-6}	73.6157	**63.4007**-85.4766	60.5748
AUC_{6-t}	95.2177	90.0683-100.6616	25.4062
AUC_{0-inf}	92.1643	88.0195-96.5042	20.2766
AUC_{0-12}	88.7273	83.8021-93.9420	22.0737
AUC_{12-t}	96.4002	89.8263-103.4553	30.6425

For AUC_{0-t}, AUC_{0-inf}, AUC_{6-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

For AUC_{0-6} the 90% confidence interval for the ratio of the test and reference products fell outside the widened range of 69.84-143.19%.

Sensitivity analysis of partial AUCs

To further support that therapeutic equivalence can be concluded despite the difference in early AUC observed in the fed study, the applicant has performed a *post hoc* analysis with other partial areas believed to be more relevant to the site of action. The applicant has thus performed a *post hoc* sensitivity analysis on three types of pAUCs (early partial areas, potential clinically relevant partial areas and late partial areas) from the fasted and fed study. The clinically relevant areas are ileum and ascending colon. In order to establish the different potential clinical pAUCs, the applicant has used results from Edsbäcker *et al* 2003 with data on gastrointestinal transit showing when the reference product Entocort reaches colon in fasted and fed state and percentage of absorption in different regions.

Table 5. A graphical representation of the limits covered normal ranges and extended ranges

	Type or area	Early partial areas	Clinically relevant partial areas	Late partial areas
FASTED	Normal range (covering 95% of cases (from lower to upper ranges)	0 to **2.5h**	**2.5**-4.0 to **14**-20h	**14**h to 48h
	Extended range investigated	0 to 12 h	1h to 14-48 h	7h to 48h
FED	Normal range (covering 95% of cases (from lower to upper ranges)	0 to **4.0h**	**4.0** - 5.25 to **16**-24h	**16**h to 48h
	Extended range investigated	0 to 12h	1h to 16-48h	7.5 to 48h

Results
Fasting and Fed: All potential clinically relevant partial areas comply within the acceptance interval of 80.00-125.00%

Fasting and Fed: All considered late partial areas comply within the acceptance interval of 80.00-125.00%.

Fasting and Fed: Early partial areas are very variable, and they represent only a low percentage of total absorption. The percentage of AUC_{last} for a particular early pAUC (Fed state) can be seen in the Table 6 below.

Fasting: Bioequivalence comply for all partial areas beyond pAUC0-3.67h using widened acceptance criteria. The pAUCs beyond pAUC0-5.5h comply within the acceptance interval of 80.00-125.00%.

Fed: Bioequivalence comply for all partial areas beyond pAUC0-7h using widened acceptance criteria (except AUC0-9h). The pAUCs beyond pAUC0-10h comply within the acceptance interval of 80.00-125.00%.

Figure 3. Ratios and CI early pAUC FED

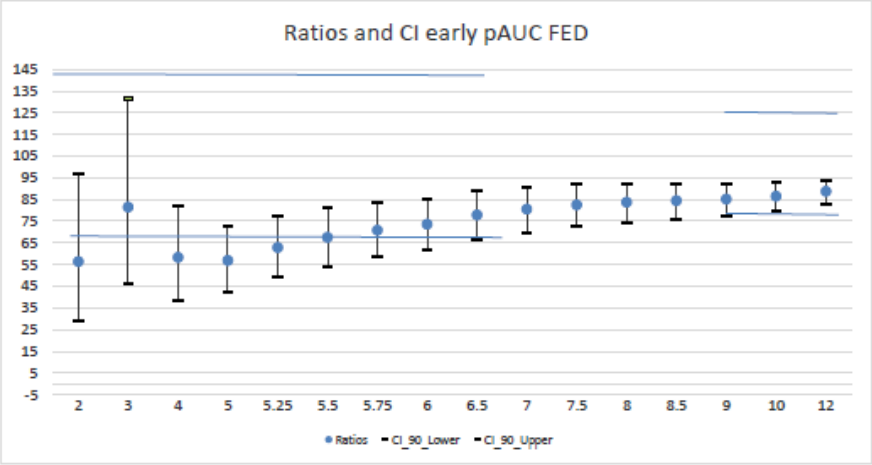


Table 6. Summary of calculated pAUC for the test product in the Fed state

Table 21. Summary of calculated pAUC for the Test drug product in the Fed state (study ARL17-380)

	AUClast	AUCall	AUC0-1	AUC0-2	AUC0-3	AUC0-4	AUC0-5	AUC0-5.25	AUC0-5.5	AUC0-5.75	AUC0-6	AUC0-6.5
N	68	68	68	68	68	68	68	68	68	68	68	68
MEAN (pg*h/mL)	11301.84	11461.28	0.00	18.83	106.46	346.93	972.92	1224.37	1505.68	1808.18	2122.24	2755.11
SD	5343.55	5262.34	0.00	81.87	326.38	733.18	1307.31	1452.06	1581.68	1703.16	1815.39	2019.42
MIN (pg*h/mL)	2878.54	3040.32	0.00	0.00	0.00	0.00	8.89	22.20	41.18	67.14	101.78	189.22
MEDIAN (pg*h/mL)	10363.38	10626.05	0.00	0.00	13.28	95.51	530.17	813.26	1074.58	1326.24	1685.66	2256.93
MAX (pg*h/mL)	29442.36	29442.36	0.00	541.35	1925.30	3739.14	5646.82	6122.51	6577.38	6994.91	7494.89	8604.49
CV%	47.28	45.91	#¡DIV/0!	434.69	306.57	211.33	134.37	118.60	105.05	94.19	85.54	73.30
GEOMEAN (pg*h/mL)	10163.95	10377.00	#¡NUM!	#¡NUM!	#¡NUM!	#¡NUM!	390.93	596.16	845.25	1118.50	1409.66	2012.87
% pAUC vs AUClast	NA	NC	0.00	0.17	0.94	3.07	8.61	10.83	13.32	16.00	18.78	24.38

	AUC0-7	AUC0-7.5	AUC0-8	AUC0-8.5	AUC0-9	AUC0-10	AUC0-12	AUC1-48	AUC2-48	AUC3-48	AUC4-48	AUC4.5-48
N	68	68	68	68	68	68	68	68	68	68	68	68
MEAN (pg*h/mL)	3366.66	3945.77	4480.11	4961.42	5402.36	6185.92	7409.99	11465.43	11446.60	11358.97	11118.50	10880.32
SD	2206.06	2374.46	2528.93	2662.50	2782.52	3004.58	3377.35	5257.64	5235.87	5167.24	5061.19	5014.29
MIN (pg*h/mL)	299.62	430.05	575.15	746.02	858.04	1048.99	1687.27	3040.32	3040.32	3040.32	3040.32	3040.32
MEDIAN (pg*h/mL)	2891.49	3572.68	4106.22	4514.90	5051.56	5713.70	7058.22	10626.05	10626.05	10603.53	10225.49	9861.18
MAX (pg*h/mL)	9630.63	10647.94	11641.75	12564.72	13431.07	15000.21	17438.08	29442.36	29442.36	29442.36	29434.03	29420.18
CV%	65.53	60.18	56.45	53.66	51.51	48.57	45.58	45.86	45.74	45.49	45.52	46.09
GEOMEAN (pg*h/mL)	2608.04	3183.68	3719.88	4210.46	4659.06	5447.37	6667.22	10384.99	10372.00	10301.65	10086.90	9855.92
% pAUC vs AUClast	29.79	34.91	39.64	43.90	47.80	54.73	65.56	101.45	101.28	100.51	98.38	96.27

Discussion and overall conclusion

The product is a locally applied and locally acting modified release product. According to Guideline on equivalence studies for the demonstration of therapeutic equivalence for locally applied, locally acting products in the gastrointestinal tract (CPMP/EWP/239/95 Rev. 1) there is a possibility that PK bioequivalence studies based on plasma levels could be used as a surrogate of equivalence in efficacy and systemic safety:

"For modified release products containing a drug being absorbed and showing systemic bioavailability, bioequivalence studies based on plasma levels could also be used as a surrogate of equivalence in efficacy and systemic safety if the systemic absorption starts at a similar site and absorption kinetics are equivalent, because the systemic absorption occurs at the sites of release. Partial AUC assessment can help to distinguish absorption caused by an early release and absorption from release at the sites of action, if:
a) absorption is not saturated at the relevant dose (shown e.g. by means of a dose-proportionality study for all the PK parameters of interest);

b) test and reference are the same dosage form;
c) test and reference exhibit similar in vitro dissolution profiles in a battery of state-of-the-art experiments (not only in the QC media and buffers at pH 1.2, 4.5 and 6.8, but also in vitro methods simulating intraluminal pH-conditions, ionic buffer strength, physiological buffer composition, mechanical stress and residence times in the human GI tract, e.g. tests in the reciprocating cylinder apparatus simulating "average" fasted subjects and also a range of "patient-specific" patterns of pH-conditions and passage times with continuous and discontinuous passage through the small intestine);
d) partial exposures and their corresponding absorption sites are well justified.

The requirements defined in the 'Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96)' should be applied. Bioequivalence should be demonstrated in single dose studies in fasting and fed state and, in case of prolonged release products with significant accumulation, also in a multiple dose study. Partial AUCs (early and late partial AUCs as defined by predefined, well justified cut-off points) should be used as primary PK endpoint in both types of single dose studies, even in case of significant accumulation when a multiple dose study is required."

To support the application, the applicant has submitted pharmaceutical quality data, two single dose bioequivalence studies in fasting and fed conditions and a *post hoc* sensitivity analysis of different partial AUCs from the performed studies. The applicant has chosen the cut-off points for the predefined partial AUCs based on t_{max} values for the reference product (ARL/17/379 - fasting: AUC_{0-4}, AUC_{4-t} and ARL/17/380 - fed: AUC_{0-6}, AUC_{6-t}).

The bioequivalence studies and their statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr) and the Guideline on the pharmacokinetics and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1). The bioanalytical methods were adequately validated in accordance with the Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2).

Single dose studies: For the predefined primary PK parameters, the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%, except for AUC_{0-4} in the fasting study and AUC_{0-6} in the fed study. For AUC_{0-6} the 90% confidence interval for the ratio of the test and reference products fell outside the widened range of 69.84-143.19%. Thus, bioequivalence for the predefined early partial AUCs has not been shown.
In the fasting study the intention to use widened criteria was only specified for C_{max} in the study protocol, if allowing for widening criteria for partial AUC, AUC_{0-4} would also be considered, however this is not strictly in accordance with guideline. The prerequisites for widening acceptance criteria are fullfilled as the study has a replicate cross-over design. The first early partial AUC was approximately 12% lower in fasting study and 27% lower in fed study for the test product compared to the reference product.

Multiple dose study: No multiple dose study was performed by the applicant. For the single dose studies in fasting and fed state, the mean $AUC_{(0-\tau)}$ after the first dose covers more than 90% of mean $AUC_{(0-\infty)}$ for both test and reference in the fed study and it is slightly below 90% in the fasting study. There is no indication of major accumulation systemically, as $AUC_{(0-\tau)}$ in the single dose studies is almost 90% of AUC_{inf}. Thus, it is agreed that a multiple dose study can be waived. The applicant has also provided published PK data for the reference product. The PK of budesonide was investigated in patients with Crohn's disease after single dose and after repeated administration of 4.5 mg twice daily (Entocort CR capsules). After multiple doses, no accumulation of budesonide was seen. The mean plasma concentration of budesonide after repeated administration was similar at 0 and 12 h, suggesting that steady-state had been achieved. In the same time the mean plasma concentration at 12 h after dose administration was almost the same after single dose and after repeated administration, indicating no accumulation.

In order to confirm that partial AUC assessment can help to distinguish absorption caused by an early release and absorption from release at the sites of action and that PK data can be used as a surrogate for equivalence, the applicant has provided the following justifications based on the four guideline criteria (a-d described above):

a) Absorption is not saturated at the relevant dose.
The applicant has provided a summary of published PK data for budesonide modified release capsules. In a study with healthy volunteers, plasma concentrations of budesonide were assessed after 5 days of administration of Entocort 3 mg delayed release capsules at three dose levels (3 mg, 9 mg and 15 mg). Dose-proportionality of the main pharmacokinetic parameters was demonstrated. There were no significant differences in dose-adjusted 0-24 hours areas under the plasma concentration curve or maximum plasma concentration. After multiple doses, no accumulation of budesonide was seen in a study with Crohn's disease patients. The mean plasma concentration of budesonide after repeated administration of 4.5 mg twice daily (CR capsules) was similar at 0 and 12 h (1.05 vs. 0.87 nmol/L, respectively), suggesting that steady-state had been achieved. In the same time the mean plasma concentration at 12 h after dose administration was almost the same after single dose (0.91 nmol/L) and after repeated administration (0.87 nmol/L), indicating no accumulation. The published data on budesonide indicate that no significant accumulation was observed. Thus, there are no indications that the absorption is saturated at the relevant dose.

b) Test and reference are the same dosage form.

c) Similar *in vitro* dissolution.
To show similarity with the reference product, a thorough investigation has been performed regarding *in vitro* dissolution profiles simulating intraluminal pH-conditions, ionic buffer strength, physiological buffer composition, mechanical stress and residence times in the human GI tract. Comparisons were made with the reference product. All comparisons showed equivalence between the test and reference product.

d) The partial exposures and their corresponding absorption sites should be well justified.
The applicant has chosen the cut-off points for the predefined partial AUCs based on t_{max} values for the reference product. According to the guideline, the justification of the chosen cut-off time is expected to be related to the corresponding absorption site. This may be a reasonable justification of a cut-off, but it is acknowledged that the "early partial AUC" represents a relatively low percentage of the total absorption (around 12-14% in the fasting study and 19-21% in the fed study) and mainly represents absorption before the formulation reaches the desired site of action. Thus, most of the drug absorption, and the absorption that is a surrogate of the concentration at the local effect site, is represented by the large "late partial AUC".

To further support that therapeutic equivalence can be concluded despite the difference in early AUC observed, the applicant evaluated other partial areas believed to be more relevant to the site of action. The analyses of different partial AUCs from the performed studies are acknowledged. The approach appears scientifically reasonable, and it is agreed that the intermediate intervals studied may provide additional information on budesonide absorption from the site of action. The analyses show that if the earliest time points are disregarded, which may correspond to time points before the formulation has reached the site of action, bioequivalence is shown for most partial AUCs in both studies.

The analyses also illustrate that the predefined early AUC is very variable and represents a relatively low percentage of the total absorption, meaning that even though the difference in absorption between test and reference in the first hours in absolute terms is small, it causes a large impact on the ratio between test and reference. This illustrates one reason for the difficulty to show equivalence using the bioequivalence margins, and it can be argued that this difference may potentially be of minor importance due to the small amount absorbed. Early absorption is also dependent on the events within the gastrointestinal tract such as variability in the gastric emptying.

It can be argued that most additional analyses are not fully acceptable, and appear partly being data-driven. Especially with regard to the population with ileal disease only, the appropriateness of the chosen (additional) early time-intervals are not considered fully appropriate. However, acceptance of the data can be based on the fact that the early fraction of absorbed budesonide rather relates to safety, and the demonstrated statistically significant lower absorption in the 0-6 hours interval in the fed state does not indicate concern. The demonstration of keeping within the equivalence ranges in the 4-t, and 6-t sufficiently reassure about efficacy.

It can thus be concluded that the additional analyses performed *post hoc* are of scientific interest and give supportive information on the differences in early absorption between the formulations, and suggests similarity between the formulations at time points corresponding approximately to the time when the formulation is expected to be present at the site of action.

To further support that therapeutic equivalence can be concluded despite the difference in early AUC observed, the applicant has compared fraction absorbed of reference vs test product. The cumulative absorption profiles were compared for both products in fasting and fed conditions. No initial burst release is observed in the profiles, and it can be observed that the differences in fraction absorbed between test and reference products in fasting conditions are similar to the differences observed between the two products in fed conditions. The reference product can be taken irrespective of food intake. The applicant has also reviewed and discussed available clinical data for different modified-release forms of budesonide and the relationship between different release characteristics, PK profile and dose-response efficacy relationship. The conclusion made by the applicant that the observed difference in early drug release between reference and test product is not expected to affect efficacy and safety of the product is supported. The differences in PK profile at the early time points between the reference product and test product in fed conditions are not expected to affect efficacy or safety, mainly because the clinically relevant area of action is reached at the later time points.

In summary, in accordance with the Guideline on equivalence studies for the demonstration of therapeutic equivalence for locally applied, locally acting products in the gastrointestinal tract, the applicant has sufficiently justified that it is acceptable to demonstrate therapeutic equivalence for this locally applied, locally acting GI product with modified release based on pharmaceutical quality data and *in vivo* PK data in fasted and fed conditions.

Based on the submitted pharmaceutical quality data and *in vivo* PK bioequivalence studies in fasted and fed conditions with additional analyses of different partial AUCs, equivalence regarding efficacy and systemic safety has been demonstrated despite the difference in early AUCs between test product and reference product.

Pharmacodynamics/Clinical efficacy/Clinical safety

No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. As this is a hybrid application for a locally applied and locally acting product, containing the same chemical entity as the reference product, it is acceptable to demonstrate therapeutic equivalence with in vitro equivalence tests or PK bioequivalence studies. In this case bioequivalence test have been performed. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

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 Budaxiro.

Safety specification

Table SVIII.1: Summary of safety concerns (*)

Summary of safety concerns	
Important identified risks	- None
Important potential risks	- None
Missing information	- None

(*) The list of safety concerns is in line with the one published at: CMDh/330/2015,Rev31. April 2021

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.

Summary of the RMP
The submitted Risk Management Plan, version 0.1, signed 17 January 2023, is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

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 PlL 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.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Budaxiro, is found adequate. There are no objections to approval of Budaxiro, from a non-clinical and clinical point of view. Based on the submitted pharmaceutical quality data and *in vivo* PK bioequivalence studies in fasted and fed conditions with additional

analyses of different partial AUCs, equivalence regarding efficacy and systemic safety has been demonstrated despite the difference in early AUCs between test product and reference product. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The decentralised procedure for Budaxiro, 3 mg, Modified-release capsule, hard was positively finalised on 2024-02-15.

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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