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Obesity and Pediatric Drug Development

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Abstract

There is a shortage of dosing guidelines for use in obese children. Moreover, the impact of obesity on drug safety and clinical outcomes is poorly defined. The paucity of information needed for the safe and effective use of drugs in obese patients remains a problem, even after drug approval. To assess the current incorporation of obesity as a covariate in pediatric drug development, the pediatric medical and clinical pharmacology reviews under the FDA Amendments Act (FDAAA) of 2007 and the FDA Safety and Innovation Act (FDASIA) of 2012 were reviewed for obesity studies.

FDA labels were also reviewed for statements addressing obesity in pediatric patients. Forty-five drugs studied in pediatric patients under FDAAA were found to have statements and key words in the medical and clinical pharmacology reviews and labels related to obesity. Forty-four products were identified similarly with pediatric studies under FDASIA. Of the 89 product labels identified, none provided dosing information related to obesity. The effect of body mass index on drug pharmacokinetics was mentioned in only 4 labels. We conclude there is little information presently available to provide guidance related to dosing in obese pediatric patients. Moving forward, regulators, clinicians and the pharmaceutical industry should consider situations in drug development where the inclusion of obese patients in pediatric trials is necessary to facilitate the safe and effective use of new drug products in the obese pediatric population.

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Keywords

Obesity; Pediatrics; Drug development

INTRODUCTION

The prevalence of childhood obesity has rapidly increased over the past two decades, resulting in a considerable portion of the pediatric population being classified as overweight or obese [1]. Unfortunately, the impact of obesity on exposure, efficacy and safety of commonly used drugs within the field of pediatrics and its subspecialties' have yet to be systematically considered and investigated. Optimal drug dosing in obese pediatric patients is typically derived from obese adult data [2].

Obesity not only increases the total fat amount, but also lean body mass. The percentage of fat tissue however increases more than lean body mass [3]. In addition, a higher perfusion of lean tissue causes a rapid distribution of compounds into tissues and for highly lipophilic drugs an increase in the volume of distribution (Vd) should be expected. Hydrophilic drugs have not shown a significant difference in Vd between obese and non-obese individuals [4].

Obesity also influences the total body clearance (CL) of drugs [4, 5]. Obese patients have a larger kidney size which may contribute to an increased CL [5,6,7]. Glomerular filtration increases in obesity resulting in an increased CL of renally excreted drugs. Tubular secretion and reabsorption may vary (increased vs. decreased) which suggests that renal CL may also be different in obese individuals [7].

The incidence of fatty liver and non-alcoholic fatty liver disease (NAFLD) is also high in these individuals which may have a potential negative impact on hepatic CL. In obesity, glucuronidation is likely to be induced [8, 9]. Sulphation has not been examined in obese humans, but in obese rats it is decreased, increased or not affected. [10]. The activity of CYP2E1 is higher in obese patients in comparison with normal weight subjects [11]. Fatty infiltration of the liver could be the underlying cause of increased CYP2E1 activity in obese patients [12]. Insulin resistance may also play a role in the increased activity of CYP2E1 [13].

With the preponderance of evidence suggesting an impact of obesity on drug therapy and the epidemic of pediatric obesity in the US population, obesity has been incorporated into some pediatric drug development trials under the FDA Amendments Act (FDAAA) of 2007 and the FDA Safety and Innovation Act (FDASIA) of 2012. The objective of this study was to examine this incorporation of obesity into pediatric studies and dosing recommendations under FDAAA and FDASIA.

METHODS

This study did not require IRB approval or informed consent/assent as the methods involve government work that has been cleared by all relevant FDA offices and co-authors.

Medical and clinical pharmacology publically-available reviews were searched using the search terms “obesity”, “obese”, “overweight”, “body mass index” and “BMI”. The timeline for products studied in pediatric patients within the FDAAA and FDASIA drug lists were (2007-2012) and (2012-2016), respectively. We also queried FDA drug labels that contain obesity- related content by searching the same terms at Drugs@FDA, from September 2007 onwards. Our purpose was to review labels of drugs studied in pediatric patients for information on potential obesity-related changes in drug safety, efficacy, PK and dosing information that could be applied to pediatric individuals. Data validation for each drug were conducted using an Action Wizard on Adobe Acrobat X Pro [WindJack Solutions, Inc.]. The Action Wizard highlighted each incidence of every search term and linked them to a comment. Each comment was reviewed for relevance and selected content relative to our search terms were represented in a table format.

RESULTS

FDAAA and FDASIA

Among the reviewed data including labeling information for the 164 products on the FDAAA drug list, 45 were positive for our chosen keywords and qualified for review. As of October 11th, 2016, the FDASIA drug list contained 44 products with the predefined search terms. Correspondingly, we searched for labeling information of the combined 89 selected products. Of the 45 products identified in FDAAA, 31 had the key terms in the reviews and labels, 12 had key terms in the reviews only, and 2 had key terms in the labels only. Of the 44 products identified in the FDASIA listing, 28 products had key terms in both the review and the label, and 16 had key terms in the reviews only. See Tables 1 and 2 [14] for an abbreviated content review of the FDAAA and FDASIA listings.

Drugs@FDA

Among the total of 89 qualified products studied in pediatric patients from September 2007 to October, 2016 searched at Drugs@FDA, no specific dosing information was provided in regards to obesity. For many products, obesity was described as a risk factor for cardiovascular adverse events, lactic acidosis, or diabetes. Obesity is also described as a side effect of a product, especially antipsychotics.

Frequently, BMI was used to describe the study subject demographics, as a categorical measure, a safety monitoring parameter, or for growth patterns. The effect of BMI on drug PK was mentioned in four products; insulin aspart: AUC and Cmax are not affected by BMI, but CL decreased in BMI > 32 kg/m²; fluticasone: BMI/weight has no effect on PK; entecavir: lower AUC observed in higher weight adults and adolescents; levonorgestrel: BMI variance does not affect CL. In some products, BMI has been used as an exclusion or inclusion criteria in the clinical trial.

Given current speculation on the efficacy of obese women taking oral contraceptives, it is not surprising that contraceptive products contain specific language about the effect of BMI/weight on efficacy or safety. For example, the intrauterine product levonorgestrel included obese women in a Phase III trial and states in the product label that there is no apparent

effect of BMI or body weight on its contraceptive efficacy. The emergency contraceptive product ulipristal states a higher pregnancy rate in a BMI > 30 kg/m². In contrast, studies of norethindrone acetate excluded women with BMI > 30 kg/m², and this is reflected in the product labeling by the statement that the efficacy in women with a BMI > 30 kg/m² has not been studied. Other obesity-related content was featured in the insulin glulisine study, in which weight gain was observed in an obese patient; and in the tocilizumab study as death was reported in an obese 3-year-old.

DISCUSSION

The epidemic of pediatric obesity in the U.S. has led to the indirect incorporation of obesity into pediatric drug development trials in the past decade. We have identified a number of references to obesity in both medical and clinical pharmacology reviews and in labels for products studied under FDAAA and FDASIA. However, the information provided is highly variable and obesity is not directly addressed in most pediatric drug development programs.

Since obese patients exhibit increased adipose and lean tissue mass, dosing weight determinations may be quite difficult. A multitude of weight categories including total, ideal and lean body weight can be used for dosing, although the use of total body weight may yield exaggerated dose response of some potent drugs. For example, total body weight propofol dosing in overweight and obese children has been shown to correlate with pre-incisional hypotension in the intraoperative setting [15]. There are presently no clear dosing guidelines for obese pediatric patients. A recent literature search by the Pediatric Trials Network presented at the 2012 NICFID Best Pharmaceuticals Children's Act meeting identified 1712 articles on the topic of childhood obesity and dosing data. Among 22 drugs with PK data available, 41 % demonstrated clinically significant PK changes in obese children. Over 80% of the products were dosed by total body weight or unadjusted body surface area, resulting in supra or sub-therapeutic exposures in 44% of the studies. Although smaller clinical studies have begun to examine obesity PK [16], the relationship between pediatric obesity and drug response, including efficacy and safety, has not been thoroughly elucidated.

Harskamp-van Ginkel et al. recently performed an evidenced based review of data to determine the effect of obesity on drug disposition in children and concluded the lack of information regarding this relationship may potentially hinder clinical decision-making and optimal care of pediatric obese patients [17]. They summarized that 65% of the captured database drugs reviewed showed clinically significant PK alterations in obese children.

Clinical Applications

Practitioners are forced to estimate or derive dosing regimens that may not be reliable or safe because there are no systematic dosing guidelines for these vulnerable patients. The physiological differences between obese and normal weight individuals of the same age, gender and height, can greatly impact drug exposure [18], potentially altering the safety profile and effectiveness of drugs when they are used in obese patients at doses that were identified in the non-obese. One rationale for poor outcomes (for excess treatment related toxicities) in obese patients may be due to differences in drug distribution volume,

particularly with regard to solubility of the agent in water vs. lipid [19]. Clinical outcome data for obese adults has been well documented due to the coexistence of chronic comorbid disease states. Many authors have considered the relationship between adult obesity and increased morbidity and mortality [20]. Although obesity rates remain high in the pediatric population and childhood obesity is also linked to comorbid disease, there is a significant knowledge gap between childhood obesity and clinical outcome data. Several smaller studies have suggested higher hospital charges and longer hospital stays for obese children [21]. Length of hospital stay has been shown to be increased in obese kids (2-18 years) with critical illness [21, 22]. Many authors have suggested a causal correlation between childhood obesity and asthma and respiratory complications extending hospital stay and length of treatment [23, 24]. Multiple studies have cited obesity as a significant predictor of mortality. Also, the presence of chronic disease or illness seems to imply an increased risk of mortality in obese children, which parallels the observation that obese adults have a shorter lifespan [25].

Pediatric oncology: Emerging morbidity and mortality data in the field of clinical oncology shows a meaningful association between pediatric and adult obesity and poorer outcomes. Orgel et al. described a greater risk of relapse or death and the development of treatment related toxicity in pediatric patients with weight extremes and ALL [26]. They also noted that patients who attained a normal or overweight status after initiation of chemotherapy had reduced complication rates, approaching that of normal weighted patients.

In 2012, the American Society of Clinical Oncology (ASCO) Clinical Practice Guideline was published on the appropriate chemotherapy dosing for obese adult patients [27]. It recommends that full weight-based cytotoxic chemotherapy doses be used to treat obese adult patients with cancer. Because there is a dearth of information on the influence of obesity on the PK of most anticancer drugs, the guidelines also recommend further research into the role of PK for the dosing of these potent drugs in adults. In general, dose adjustment is a complex issue in the treatment of pediatric patients with chronic illness or disease, given that pharmacologic treatment may occur across a broad range of chronologic age and/or growth and development.

Pediatric inflammatory bowel disease: As another clinical consideration, the issue of poorer clinical outcomes in the obese pediatric population can be appreciated in patients with inflammatory bowel disease (IBD). Typically, IBD is associated with under nutrition. However, rates of obese IBD patients are substantial. One in 5 children with Crohn's disease (CD) and one in 3 children with ulcerative colitis (UC) are obese [28]. At diagnosis, 10% of children with CD have a BMI greater than the 85th percentile [29]. In a study of 148 adults with CD, patients who had a BMI >25 kg/m² were significantly older at diagnosis and had a shorter time to first surgery than those with a BMI <18.5 kg/m² [30]. In a multicenter cohort study of almost 1600 children with IBD, obesity and overweight status were associated with an increased need for disease-related surgery [28]. Obesity has also been associated with more active disease and risk of hospitalization [31].

Increasingly, therapies with monoclonal antibodies (MAbs), such as anti-tumor necrosis factor-alpha (TNF α) therapies, are being used to treat both CD and UC. However, there are no studies or guidelines for dosing of obese patients who need biologics. No regulatory guidelines exist for postmarketing studies of these drugs in the obese population.

About 20% of patients taking adalimumab have a loss of response requiring escalation of dosing [32]. However, loss of response and lack of effectiveness to adalimumab have been associated with high BMI in several studies [33, 34].

Infliximab dosing is based upon body weight, which might make it seem less likely that obesity would affect outcomes. However, obese patients with CD and UC (BMI > 30 kg/m²) who are naive to anti-TNF therapies also have an attenuated response to infliximab, manifested by an earlier time to dose escalation [35].

Monoclonal antibodies have a high molecular weight and are hydrophilic [36]. Emerging data suggest that there is a strong relationship between monoclonal antibody serum drug concentrations, and the ability to achieve disease remission and endoscopic healing in IBD [37, 38, 39]. A higher serum infliximab trough concentration has been associated with an increased response, both clinically and endoscopically, in adults with CD and UC [37, 38]. Higher trough concentrations of adalimumab and certolizumab pegol have also been correlated with mucosal healing in adults with CD [39, 40, 41]. There are several possible explanations why patients who are obese respond different to monoclonal antibody therapies in IBD. One potential explanation is that insufficient drug concentration is present within the tissue to block the excess of TNF α [42]. An increased level of TNF α measured in intestinal tissue has been associated with increased endoscopic disease activity in patients taking TNF α antagonists [43]. Lower levels of TNF α gene expression in colorectal mucosal biopsies has been associated with improved rates of remission after induction in adults with UC [44]. Creeping mesenteric fat over the bowel serosa in CD has been shown to be a major producer of pro-inflammatory adipocytokines, including TNF α [45]. Increased TNF α mRNA is expressed by adipocytes in obese adults, with an associated increase in production of TNF α [46]. Further studies are needed to evaluate the use of TNF α measurement in intestinal biopsies and how mesenteric fat affects TNF α levels in intestinal tissue. Infliximab is administered intravenously and is known to bind to both membrane bound and circulating TNF α [47]. Dosing of infliximab is weight-based, and there is an assumption that exposure in relation to body weight is linear. However, the influence of weight on the CL of MAbs (and hence area under the curve) is not linear [42]. MAbs are cleared by the cells of the reticuloendothelial system after binding to Fc receptors. Clearance of MAbs is not affected by renal or hepatic functions [42]. Ordas et al (2012) evaluated factors affecting the PK of MAbs, and found that a high BMI may increase CL. Other factors that may increase CL include a high baseline C-reactive protein and low serum albumin. The presence of anti-drug antibodies also increases CL, while concomitant use of an immunomodulator decreased monoclonal antibody CL and reduced anti-drug antibodies [42]. Whether obesity impacts the likelihood of forming anti-drug antibodies is unknown.

Few studies have investigated how systemic absorption and bioavailability of subcutaneously administered drug is affected by fat [48]. Adalimumab, a subcutaneously-administered drug,

is not dosed based upon body weight, except when differentiating children greater than or less than 40 kg of body weight; adult patients receive a fixed dosing regimen. Pharmacokinetic studies have not assessed the effects of obesity on circulating serum levels of adalimumab.

Given the importance of adequate bioavailability of MAbs, more studies on the PK and pharmacodynamics of biologics in obese IBD patients are urgently needed. Additional studies are also needed to define optimal serum or intestinal mucosal drug concentrations of biologics. A standard dosing and escalation protocol in obese patients may be missing the effectiveness mark. Understanding the impact of pediatric obesity on drug absorption, distribution, elimination, efficacy, and safety may aid in the development of specific dosing recommendations for obese children.

Conclusions

Presently very little PK data is available to guide dose adjustment in the pediatric obese population. Of the 89 products we identified since 2007 that had key terms in reviews or labeling, none provided dosing information related to obesity. The effect of BMI on drug PK was mentioned in only 4 labels.

Additionally, there is little guidance available concerning the recruitment of obese subjects for pediatric drug trials and product development. The simple inclusion of a homogenous cohort of obese children may not be sufficient as degrees or severity of obesity exist within this population. For example, at Children's National Health System in Washington, DC, our weight loss surgical program includes children and adolescents who have weight categories greater than the 99th BMI percentile. However, the American Academy of Pediatrics defines a pediatric-aged patient with an age- and sex-matched BMI of greater than or equal to 95th percentile as overweight or obese.

Another issue to consider during the product development process is situations in which obese subjects may be considered as a special population group. For example, nonalcoholic steatohepatitis (NASH) is associated with varying degrees of obesity and many morbidly obese adolescents have this diagnosis prior to surgery. It has been shown that morphine PK in adults with NASH is altered due to liver impairment, suggesting that dose adjustment of potent narcotics can be needed during pain management [49]. This change in morphine PK would have major implications in the clinical setting to avoid adverse clinical events including exacerbation of obstructive sleep apnea (OSA) after surgery.

The clinical applications presented underscore the significant need for regulated dosing considerations for the obese pediatric population.

Moving forward, regulators, clinicians and the drug industry should discuss the situations in drug development where the inclusion of obese patients in pediatric trials would be necessary to understand the safe and effective use of new drug products in these special patients.

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TABLE 1

Summary – Food and Drug Administration Amendments Act/(FDAAA) list¹⁴

Trade Names (generic)	Safety/Efficacy Reviews	Labeling Information
Axert (almotriptan)	Obesity mentioned as a risk factor for CAD	Obesity mentioned as a risk factor for CAD
Arimidex (anastrozole)	Adverse events seen in association with obesity	No mention of search terms
Ability (aripiprazole)	No mention of search terms	a. Obesity /overweight as risk factor for type 2 diabetes b. Obesity as an infrequent adverse drug event c. Deltoid and gluteal administration instructions specified for obese patients d. Exploratory subgroup analysis conducted by BMI
Atacand (candesartan)	Greater level of obesity cited in older versus younger study population	No mention of search terms
Depakote ER & Sprinkles (divalproex)	BMI/obesity used as a metric for adverse events	No mention of search terms
Inspira (eplerenone)	Recruited patients diagnosed with primary hypertension or obesity	No mention of search terms
Natazia (estradiol valerate & estradiol valerate/dienogest)	a. BMI > 30 kg/m ² as an exclusion criteria b. Better efficacy results seen in Europe due to better compliance and lower BMI c. Little change in BMI categories from screening to final examination were seen in a large population of volunteers d. Weight increase listed as common adverse event e. Case report of a patient with a BMI of 31.4kg/m ² experiencing an MI while on this drug f. BMI observed for safety g. BMI as covariate for venothromboembolism risk estimates	a. The efficacy of Natazia not evaluated in women with a BMI of >30 kg/m ² . b. Obesity as a risk factor for developing blood clot while taking Natazia
Intuniv (guanfacine)	No mention of search terms	Effects seen on weight gain
Apidra (insulin glulisine)	Weight gain observed in an obese patient	Euglycemic clamp study in obese, non-diabetic subjects showed that the more rapid onset of action and shorter duration of activity of Apidra and insulin lispro compared to regular human insulin were maintained in an obese nondiabetic population
Kaletra (lopinavir&ritonavir)	Obesity cited as CVD risk factor in pediatrics	Redistribution/accumulation of body fat including central obesity has been observed in antitviral therapy
Maxalt-MLT (rizatriptan)	Obesity related to abnormal ALT	a. Obesity as a CVD risk factor b. Weight-based dosing
Crestor (rosuvastatin)	a. Obesity cited as a CVD risk factor b. BMI as an assessment of impact of treatment on growth c. Cardiovascular event risk reduction consistent in BMI subgroup	Crestor has no effect on BMI in pediatrics (10-17 years old)
Actemra (tocilizumab)	Obese 3 year old case report (death)	Weight-based dosing
Diovan (valsartan)	21.5% of the randomized population had a history of obesity in the study, but no dosing adjustment mentioned	a. Renal and urinary disorders, and essential hypertension with or without obesity were the most common underlying causes of hypertension in children enrolled. b. Weight-based dosing for pediatric hypertension indication
Novolog (insulin aspart)	a. AUC and Cmax of NovoLog were generally unaffected by BMI. b. CL reduced by 28% in patients with BMI >32 kg/m ² compared to patients with BMI <23 kg/m ²	a. AUC and Cmax of NovoLog were generally unaffected by BMI. b. CL reduced by 28% in patients with BMI >32 kg/m ² compared to patients with BMI <23 kg/m ²
Alvesco (ciclesonide)	Obese adult female case report (death)	No mention of search terms

Trade Names (generic)	Safety/Efficacy Reviews	Labeling Information
Nexium I.V. (esomeprazole)	a. Overweight or obese patients may experience more gastrointestinal reflux b. Unlikely that BMI will affect pharmacokinetics	No mention of search terms
*Afinitor (everolimus)	Two obese patients at baseline had large weight loss and highest percentile of adverse events	No mention of search terms
Zyprexa (olanzapine)	Treatment group has greater weight gain and increase in BMI than placebo	Weight gain as a side effect of Zyprexa
Vyvanse (lisdexamfetamine)	a. Overweight (BMI > 97 percentile) as a study exclusion criteria b. BMI as safety assessment	Not a treatment of obesity
Seroquel (quetiapine)	a. Weight gain/BMI increase as a side effect b. CL/F tended to decrease with BMI	BMI change as measure of weight gain and as safety assessment Obesity reported as a risk factor for diabetes
Daytrana (methylphenidate transdermal system)	Overweight/BMI > 95 percentile adolescent excluded	No mention of search terms
Kapvay (clonidine)	BMI > 5 percentile included in the study	No mention of search terms
Welchol (colesevelam)	No clinically meaningful differences between BMI subgroups (<25 kg/m ² vs ≥ 25 kg/m ²) in the incidence rates or types of adverse reactions	Consistent effects on A1C across subgroups of BMI
Prezista (darunavir)	Darunavir effect on growth (BMI, weight, height) was assessed	a. Redistribution/accumulation of central obesity has been observed in patients receiving antiretroviral therapy b. Weislit-based dosing in pediatric patients
desmonessinacetate	Study population reported with BMI	No mention of search terms
Safyral (drospirenone/ethinyl estradiol/levomefolate)	a. Two studies combined BMI inclusion criteria 18.5 – 35 kg/m ² b. Obesity as a risk factor for developing blood clots while on Safyral	Obesity as a risk factor for developing blood clots while on Safyral
Beyaz (drospirenone/ethinyl estradiol/levomefolate)	a. Two studies combined BMI inclusion criteria 18.5 – 35 kg/m ² b. Obesity as a risk factor for developing blood clots while on Beyaz	a. Women BMI > 35kg/m ² excluded from the trials b. Obesity as a risk factor for developing blood clots while on Beyaz
Makena (hydroxyprogesterone caproate)	a. BMI stratified to analyze the dose-plasma concentration time relationship of drug. b. BMI-dependence of apparent clearance as a pharmacokinetic covariate	Mean BMI, 26.9 kg/m ² of study group cited to evaluate reduction of risk of preterm birth
Keppra (levetiracetam)	BMI as demographic feature	Weight-based dosing in pediatric patients
*norethindrone and ethinyl estradiol chewable tablets and ferrous fumarate chewable tablets	a. BMI 30-35kg/m ² subgroup analysis: higher Pearl Index of 2.89 if BMI >kg/m ² , but not statistically significant b. Efficacy in BMI>35kg/m ² not studied	a. Obesity as a risk factor for developing blood clots while on birth control b. The efficacy in women with a body mass index (BMI) of >35kg/m ² has not been evaluated.
Dulera (mometasone and formoterol)	a. Gender, race, BMI did not appear to impact study results b. BMI 18–29 kg/m ² as study inclusion criteria	No mention of search terms
Xolair (omalizumab)	Need more data on BMI as it relates to response and dosing cited.	a. Weight-based dosing for asthma patients b. Covariate effect analysis showed no dose-adjustment needed per BMI for patients with chronic idiopathic urticaria
Invega (paliperidone)	a. Weight change as a side effect of Invega b. BMI as an assessment for safety c. Lower treatment effect who weighed <51kg	a. Obesity as risk factor for diabetes. Need to check glucose while taking atypical antipsychotic b. Weight-based dosing in pediatric patients
Zenpep (pancrelipase)	a. Weight loss/gain and BMI as secondary endpoints. b. No clinically significant changes in mean weight and BMI from screening to end of study and between treatment periods	Weight-based (actual body weight) dosing in pediatric patients
Ultresa (pancrelipase)	BMI mentioned as inclusion criteria	Weight-based dosing in pediatric patients

Trade Names (generic)	Safety/Efficacy Reviews	Labeling Information
Protonix (pantoprazole)	a. No negative impact on growth in pediatric patients measured with BMI b. BMI and weight measured during pretrial screening period and at final visit – no significant changes seen	Weight-based dosing in pediatric patients
Viread (tenofovir)	BMI as demographic feature	a. Risk of lactic acidosis if obese and/or very overweight b. Redistribution/accumulation of central obesity has been observed in patients receiving antiretroviral therapy c. Weight-based dosing in pediatric patients
Topamax (topiramate)	BMI and Z-score measured in pediatrics to check growth pattern and safety analyses	Weight-based dosing in pediatric patients
*Ella (ulipristal acetate)	a. Effectiveness seems to be attenuated in BMI >30 kg/m ² (the sample size of BMI>30 kg/m ² is rather small) b. A trend of decreasing exposure of ulipristal acetate with increasing BMI	Higher pregnancy rate in BMI > 30kg/m ²
Geodon (ziprasidone)	Weight/BMI change as a result of Geodon (no difference between placebo)	a. BMI as a monitoring parameter for the side effect weight gain b. Obesity as a risk factor for diabetes (monitor signs and symptoms of hyperglycemia)
Zomig (zolmitriptan)	Strongly recommend that 'triptans' are not prescribed to patients with risk factors for undiagnosed CAD (obesity) without first undergoing a thorough cardiovascular evaluation.	Obesity as a risk factor for heart disease.
Intelence (etravirine)	a. BMI as an assessment on growth b. BMI, as a pharmacokinetic covariate, with other body size descriptors may explain a certain part of the variability in CL/F.	Fat redistribution observed in antiviral therapy Pediatric weight-based dosing (max=adult dose)
Flovent HFA (fluticasone)	BMI/weight had no effect on pharmacokinetics	No mention of search terms
Gadavist (gadobutrol)	Weight-based dosing	Weight-based dosing for pediatric patients

CAD-Coronary Artery Disease; BMt-Body Mass Index; CL/F-Clearance; Vd-Volume of distribution; ALT-Alanine Aminotransferase; CVD-Cardiovascular Disease; AUC-Area Under Concentration Curve; Cmax-Maximum Concentration

TABLE 2

Summary – Food and Drug Administration Safety and Innovation Act /(FDASIA) drug list¹⁴

Trade Names (generic)	Safety/Efficacy Reviews	Labeling Information
Saphris (asenapine)	a. Obesity as a criteria of type II DM b. BMI does not result in clinically meaningful dose adjustment	a. Obesity as a risk factor for type II DM b. BMI as a measurement weight change b. No effect of BMI on drug exposure in special populations observed
Bloxiverz (neostigmine methylsulfate)	Obesity is an exclusion criteria in the clinical studies	Weight-based dosing
Precedex (dexme detomidine)	Obesity as an exclusion criteria	Weight-based dosing
Liletta (levonorgestrel)	a. Phase III trial included obese women b. No difference in contraceptive efficacy based on BMI c. Subset PK study included obese patients	Obese patients studied in clinical trials. No apparent effect of BMI or body weight on contraceptive efficacy
Namenda XR (memantine)	BMI/Overweight/Obese used as a safety endpoint measurement	Safety and effectiveness in pediatric patients have not been established.
ProAir RespiClick (albuterol sulfate)	Overweight/obese adolescents enrolled in bioanalytic method study	No mention of search terms
Baraclude (entecavir)	a. Lower AUC observed in higher weight adults and adolescents b. Die covariate analysis identified body size (body weight, body surface area, body mass index) as important predictive factors of entecavir PK.	a. Obesity/overweight may be a risk factor to develop lactic acidosis or serious liver problems b. Weight-based dosing in pediatric patients
Intuniv (guanfacine)	Overweight as an exclusion criteria in a phase III study	a. Weight increase after use for 12-month: Die BMI percentile remained stable in patients at 12 months in the long-term studies compared to when they began receiving INTUNIV® b. Weight-based dosing in pediatric patients
Quartette (levonorgestrel & Ethinyl Estradiol)	a. BMI was stratified for bleeding analysis b. BMI and body weight did not result in a statistically significant effect on PK but the available data is insufficient to rule out a body weight effect on drug clearance. There was a trend for increased CL with increased body weight.	Birth control pills increase risk of blood clots, obesity is a risk factor
Asmanex FIFA (mometasone)	BMI did not appear to affect trial result	No mention of search terms
Symbyax (olanzapine & fluoxetine)	a. Weight and BMI differences between the OFC and placebo groups were statistically significant b. No additional dose adjustment based on body weight is recommended in patients 10-17 years of age on OT prolongation	Weight gain as a side effect based on BMI categories
Noxafil (posaconazole)	BMI used to describe the study population	No mention of search terms
Treximet (sumatriptan & naproxen)	BMI in demographics description	Overweight as a risk factor for heart disease
Bethkis (tobramycin)	BMI in demographics description and one of the secondary endpoints	a. Die 300 mg/4 mL dose of BETHKIS is the same for patients regardless of age or weight.
Intelence (etravirine)	BMI, as a PK covariate, with other body size descriptors may explain a certain part of the variability in CL/F. b. BMI as an assessment on growth	“Fat redistribution” as a result of taking Intelence Weight-based dosing
Dutrebis (lamivudine & raltegravir)	BMI used in inclusion criteria and matched to healthy control, but no subgroup analysis regarding BMI and dosing	a. Overweight/obese as factor to develop lactic acidosis/severe hepatomegaly b. “Fat redistribution” as a result of taking Dutrebis c. Weight-based dosing d. Seriously overweight increases risk of lactic acidosis
Aleve PM (naproxen & diphenhydramine)	BMI described in study population	No mention of search terms

Trade Names (generic)	Safety/Efficacy Reviews	Labeling Information
Invirase (saquinavir)	BMI showed significant associations with CL/F	“Fat redistribution” as a result of taking Invirase
Xolair (omalizumab)	a. There is a need for more data on BMI as it relates to response and dosing. b. BMI was identified as statistically significant covariates on PK/PD parameters and had modest ($< \pm 26\%$) effects on omalizumab trough value c. There was no impact of BMI on the efficacy of omalizumab in chronic idiopathic urticarial patients	Non-weight-based dosing for chronic idiopathic urticaria patients
Skyla (levonorgestrel intrauterine)	a. Adverse events were analyzed by age, parity, ethnicity, BMI, and time. b. No additional safety issues were identified in women with BMI over 30 kg/m ² . No evidence of differences in the pearl index based on the BMI c. BMI variance does not affect clearance; body weight was found to have the highest impact on CL.	BMI (16-5 5kg/m ²) described in study demographics
Genvoya (elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide)	a. Median BMI in study subjects was 25.9kg/m ²	a. Obesity as a risk factor for lactic acidosis/severe hepatomegaly with steatosis b. Redistribution or accumulation of body fat including central obesity have been observed in patients receiving antiviral therapy c. The efficacy and safety of GENVOYA for the treatment of HIV-1 infection was established in pediatric patients aged 12 years and older with body weight greater than or equal to 35 kg
Anthem (oblitoxaximab)	a. The applicability of the current dosing recommendation to obese subjects is unknown. b. BMI 18.5-30kg/m ² were included but treatment was not stratified based on BMI c. There was no notable effect on PK parameters conferred by BMI. d. Dosing can be based on body weight without regard to sex or BMI.	Weight-based dosing in pediatric population
Oxycontin (oxycodone)	Pneumonia, elevated glucose, pain due to sickle cell, fever and falls were reported in 14 y/o obese patient.	No mention of search terms
Fycompa (perampanel)	a. BMI 18–32kg/m ² were included b. Body weight does not result in clinically significant difference in clearance of the drug.	No mention of search terms
Risperdal Consta (Risperidone)	a. Abnormalities of glucose metabolism and “growth hormone excess” during pediatric studies with risperidone cited. b. These same patients were found to have an increase in body weight, height, and body mass index “greater than expected” for their age and gender.	a. Obesity as a risk factor for Type2 DM and glucose should be monitored closely in patients receiving antipsychotics b. When treating pediatric patients with RISPERDAL® for any indication, weight gain should be assessed against that expected with normal growth. c. Weight-based dosing for irritability associated with autistic disorder in pediatric patients
Lumason (sulfur hexafluoride lipid-type a microspheres)	a. Particular importance should be given to focal liver lesion in the context of liver steatosis when considering the obesity epidemic apparent in the pediatric population. b. With the rise in the prevalence of obesity among children, there is an increased need for proper characterization of hepatosteatosis-related changes (i.e. focal fatty infiltration and fatty nodules) and their differentiation from solid liver masses.	Safety and effectiveness in pediatric patients have not been established for use in echocardiography.
Adzenys XR-ODT (amphetamine extended-release orally disintegrating tablets)	Patients of BMI 18-32kg/m ² were included	No mention of search terms
Emend (aprepitant)	BMI was not associated with significant changes in PK parameters that would indicate a clinically relevant effect on drug exposure	a. For every 5 kg/m ² increase in BMI, AUC _{0-24hr} and C _{max} of aprepitant decrease by 11%. BMI of subjects in the analysis ranged from 18 kg/m ² to 36 kg/m ² . This change is not considered clinically meaningful.

Trade Names (generic)	Safety/Efficacy Reviews	Labeling Information
		b. Recommended dosage of EMEND in adults and pediatric patients c. 12 years of age and older and patients less than 12 years of age who weigh at least 30 kg
Teflaro (ceftaroline fosamil)	Patients exhibited a lower BMI and BSA than healthy subjects due to the inclusion of the pediatric patients.	Pediatric weight-based dosing
Tivicay (dolutegravir)	a. Objectives of reviewed clinical studies were to compare PK in hepatic/renal impairment and healthy subjects matched for BMI following oral dosing b. BMI greater than 30 kg/m ² as inclusion criteria	a. Pediatric weight-based dosing b. Redistribution or accumulation of body fat including central obesity have been observed in patients receiving antiviral therapy
Cymbalta (duloxetine)	BMI listed in the demographic features	No mention of search terms
Odefsey (emtricitabine, rilpivirine, tenofovir alafenamide)	Median BMI described in two studies	a. Obesity as a risk factor for lactic acidosis/severe hepatomegaly with steatosis b. Redistribution or accumulation of body fat including central obesity have been observed in patients receiving antiviral therapy c. Not recommended for patients less than 12 years of age or weighing less than 35 kg.
Inflectra (infliximab-dyyb)	BMI 18-29.9kg/m ² included	a. Weight-based dosing b. In children with JRA with a body weight of up to 35 kg receiving 6 mg/kg of infliximab and children with JRA with body weight greater than 35 kg up to adult body weight receiving 3mg/kg infliximab product, AUCss was similar to that observed in adults receiving 3 mg/kg of infliximab.
Lamictal (lamotrigine)	Mean change from baseline for BMI was not notable	Pediatric weight-based dosing
Delzicol (mesalamine)	BMI was described as demographic feature	5 years and older: weight-based dosing
QuilliChew ER (methylphenidate hydrochloride extended release chewable tablets)	BMI 18-30kg/m ² were included Mean BMI 25-26kg/m ² cited	No mention of search terms
Narcan Nasal Spray (naloxone)	BMI 18-30 kg/m ² were included Mean BMI = 27.1 kg/m ²	No mention of search terms
Minastrin 24 Fe (norethindrone acetate and ethinyl estradiol capsules and ferrous fumarate capsules)	BMI range 19-29.9 kg/m ² were included	a. The efficacy in women with a BMI of more than 35 kg/m ² has not been evaluated. b. Obesity as a risk factor for blood clots
AcipHex Sprinkle (rabeprazole)	BMI within a certain range were included in the studies	No mention of search terms
Cinqair (reslizumab)	a. BMI <28 kg/m ² were included b. Patients with lower BMI have higher predicted maximum FEV1 response c. Body weight is a statistically significant covariate for CI	The safety and effectiveness in pediatric patients (aged 17 years and younger) have not been established
Priftin (rifapentin)	a. Median BMI of 26kg/m ² b. BMI within certain ranges were enrolled in the studies	a. 2-12 years old, weight-based dosing for the treatment of latent tuberculosis b. The safety and effectiveness of PRIFTIN in the treatment of active pulmonary tuberculosis have not been established in pediatric patients under the age of 12.
Kovanaze (tetracaine and oxymetazoline)	a. BMI does not appear to be linked to substantial clinically significant safety concerns. b. BMI as demographic feature	KOVANAZE is not advised for use in pediatric patients weighing less than 40 kg because efficacy has not been demonstrated in these patients
Arnuity Ellipta (fluticasone furoate inhalation powder)	There was no effect of age, body weight, BMI and gender on the systemic exposure in subjects with asthma.	No mention of search terms
Dysport (abobotulinumtoxin A)	BMI as demographic feature (mean BMI 15 kg/m ²)	Dosing for pediatric lower limb spasticity is based on units per kilogram of body weight

DM-Diabetes Mellitus; BMI-Body Mass Index; AUC-Area Under Concentration Curve; OFC-Olanzapine-Fluoxetine Combination; CL-Clearance; PK-Pharmacokinetics; JRA: e-GFRs-Juvenile Rheumatoid Arthritis; BSA- Body Surface Area, AUCss- Steady State Area Under the Concentration Curve, FEV1-Forced Expiratory Volume in 1 second.

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